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CONTENTS

PAGE

The Influence of Heredity in Exophthalmic Goitre. By E. A. Cockayne, D.M., F.R.C.P. ... 227

On Pyelitis Complicated by Jaundice. By Professor E. Comby and Dr. G. O. E. Lignac ... 232

A Case of Paratyphoid B. Infection with Purpura and Specific Broncho-Pneumonia. By H. F. Jameson, M.B., B.Sc., and A. Sibly, L.R.C.P., M.R.C.S. ... 238

Observations on the Chloride, Sugar, and Calcium Contents of the Cerebro-Spinal Fluid in Children. By A. Victor Neale, M.D., M.R.C.P., and Marion S. Esslemont, B.Sc. ... 249

The Ætiology of Coeliac Disease: Preliminary Communication on the Blood Fat. By Alan Moncrieff, M.D., M.R.C.P., and W. W. Payne, M.D., F.R. ... 257

Functional Vomiting in Newborn and Premature Infants. By William Emdin, B.A., M.D. ... 262

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THE INFLUENCE OF HEREDITY IN EXOPHTHALMIC GOITRE.

BY

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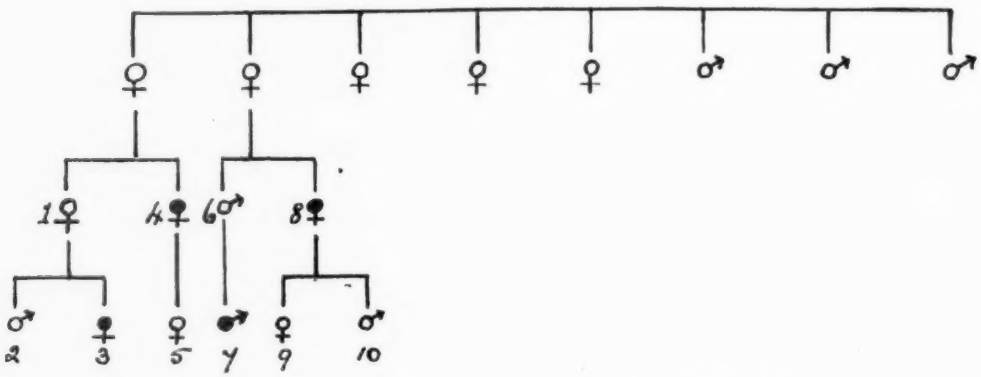
The tendency in recent years has been to look upon exophthalmic goitre as a disease due to some acquired cause such as an infection of the teeth or tonsils, or to mental worry, and to disregard the inborn liability of certain individuals to develop the condition. Sir Archibald Garrod's Huxley Lecture on Diathesis delivered last November has been a timely reminder that in many diseases not actually hereditary, an inborn weakness of some organ may be inherited and render it susceptible to some particular disorder. This appears to be true of the thyroid gland and exophthalmic goitre.

A large number of families have been reported in which more than one member of the same generation has been affected, or in which the disease has occurred in several members of successive generations. Unfortunately in very few of these families has a complete pedigree been given, but in none of those in which such a pedigree is available does the number with exophthalmic goitre correspond with that expected of a Mendelian dominant. In a number of cases it has been met with in a parent and one or more of the children, and in two, reported by Cantilena and Sottas, it affected parent, child, and grandchild. This shows that, though it does not behave strictly as a dominant, it cannot be a recessive character.

In the family I am recording there were five females and three males, all apparently healthy, in the first generation. The eldest of the daughters had two children, both girls; the elder was normal, but of her two children the first a boy, was normal, and the second, a girl of eight, whose illness I am describing later, had exophthalmic goitre; the younger had exophthalmic goitre which started at the age of forty years, and her only daughter who was twenty years of age and unmarried was healthy. The second daughter of the first generation had two children, a son and a daughter. The son is apparently normal, but his only child, a boy aged ten years, has severe Graves's disease, for which he has been treated by X-rays. Both father and son have lived for many years in Canada, so that environment can have had no influence in causing the disease in these two branches of the family. The daughter, aunt of the little boy with Graves's disease, developed Graves's disease at the age of twenty-four, and has two healthy children, a girl who was born before her mother's symptoms appeared and a boy who was born after they appeared. Unfortunately it has been impossible to obtain any information about the other members of the first generation (Fig. 1).

The girl mentioned above was aged eight years and three months, when she was seen at the Hospital for Sick Children, Great Ormond Street, on February 24th, 1927. There was a history that goitre with rapid pulse had been noticed first in the previous November. She had slight exophthalmos, von Graefe's sign, uniform enlargement of the thyroid gland, a fine tremor of the hands, and a pulse rate of 160 at rest. She was extraordinarily excitable, speaking very quickly and continually altering her position. She was thin and her weight, which had gone down, was 53 lb. Her skin was moist and she was rather flushed. She improved considerably in the hospital under the care of Dr. Robert Frew, who has kindly given me permission to publish these notes, and had no treatment there except rest in bed. She was looked after very carefully after her discharge from the hospital, and with getting up late, lying down in the afternoon, and leading a quiet life, continued to make good progress. In July, 1927, she weighed 59¼ lb.; her pulse rate was about 100 at rest though the rate increased readily after exertion or with emotion. She was much less excitable, but she still showed all the signs of the disease.

It is interesting that the phenomenon of anticipation which is so common in hereditary diseases of a degenerative nature, is also shown in this disease which belongs to another category. It is probably due to this that a much

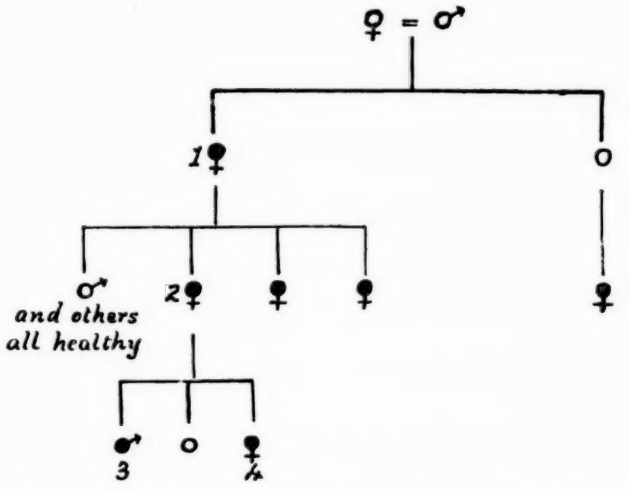


3. Onset at 7 years.
4. Onset at 40 years.
7. Onset before 10 years.
8. Onset at 24 years.

Fig. 1.—Author's Case.

higher percentage of cases in children occurs in hereditary than in sporadic exophthalmic goitre. This family adds another example of anticipation to those already published. In the family described by Zelener the disease began at the age of thirty-three in the mother, but was fully developed at twenty-seven and twenty-five in her two daughters and earlier still in her two sons. In Climenko's family (Fig. 2.) it appeared at thirty-nine in the first generation, at twenty-seven in the second, and it was already present at the ages of ten and six years in two of the children of the third generation. In Raillet's family the father did not develop Graves's disease until after the birth of his daughter, but in her case it was present at the age of seven and a half years. Solbrig describes a family in which the mother developed the disease in adult life but her son already showed the signs at eight years of age. In the family reported by Moss the mother had the disease as an adult, her eldest child, a boy of eleven years, had developed it, her second child, a girl of five, was healthy,

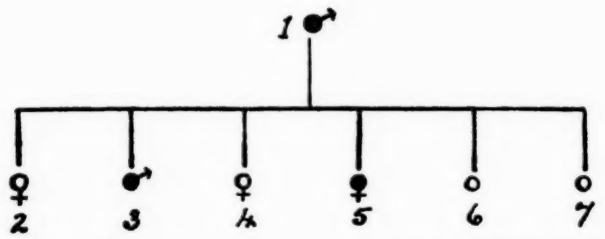
and her third child was beginning to show the early signs. Kronthal describes a family in which the mother and her twelve year old child had Graves's disease, her eight year old daughter was healthy, and five other children had died in the first years of life. Rosenberg gives an account of a family in which the



1. Onset at 39 years.
2. Onset at 27 years.
3. Disease present at 10 years.
4. Disease present at 6 years.

Fig. 2.—Climenko's Case.

father and two daughters had the disease, the younger developing exophthalmos at eight and all the other signs later ; she married a man whose mother and two sisters had Graves's disease, and of their family of eleven children ten were stillborn or died in infancy, and only one survived. In the family described



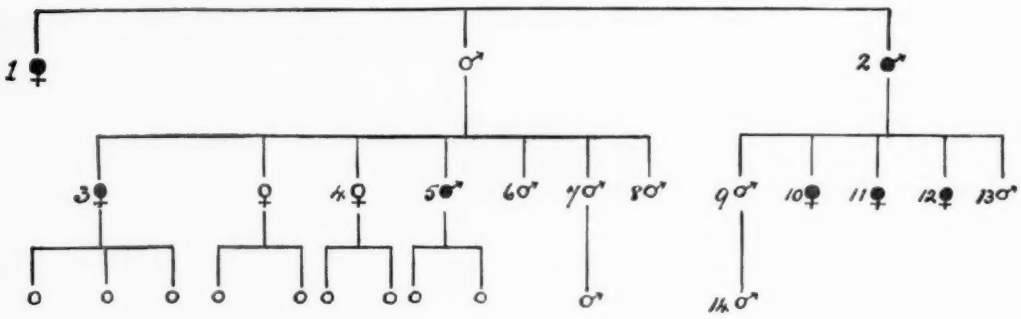
1. Aged 43, exophthalmos and nervousness.
2. Aged 19.
3. Age not stated, exophthalmos and tachycardia.
4. Aged 14, tachycardia.
5. Aged 10, typical Graves's disease.
6. Aged 6.
7. Aged 3.

Fig. 3.—Nicoll's Case.

by Nicoll (Fig. 3.), the father developed exophthalmos and nervousness as an adult but no tachycardia, his eldest son had exophthalmos and tachycardia, his second daughter aged fourteen had tachycardia, his third daughter aged ten had all the signs of Graves's disease, and his three remaining children were

normal. In the case of the families collected by Curtin, though the age of onset is not given, it is noteworthy that in the second generation the disease was frequently present in childhood or at puberty. I have been unable to obtain access to the publication in which Dubreuil-Chambardel gives an account of a family in which four out of eight members were affected in three generations, but the fact that two were children, aged seven and four years respectively, suggests that this family also exhibited the phenomenon of anticipation.

Even in hereditary cases the disease may only become manifest after puberty and sometimes not until middle age or later. This is well shown in the family described by Osterreicher. Graves's disease appeared in three generations and affected eleven out of sixteen members of the family, but the symptoms did not develop until late adult life. In the family described



1. Died at 70 years.
2. Died at 57 years.
3. Aged 49.
4. Aged 43.
5. Aged 39.
6. Aged 35.
7. Aged 30.
8. Aged 24.
9. Aged 45.
10. Died of pulmonary tuberculosis, aged 36.
11. Aged 41, no children, married.
12. Aged 29, no children, married.
13. Killed in 1914.
14. Aged 20.

Fig. 4.—Souques and Lermoyez Case.

by Souques and Lermoyez (Fig. 4.), the disease developed before middle age. In other hereditary cases the onset is earlier, and the disease may appear in childhood, but it is almost unknown as a congenital malady. Of the two cases of congenital Graves's disease recorded as having occurred in the children of mothers suffering from the same condition, only that reported by Clifford White seems to have been a genuine example. The one reported by Schmauch appears to have been a case of oxycephaly in the baby of a woman with Graves's disease.

Transmission frequently occurs through apparently normal individuals and the disease affects grandparent and grandchild, or aunt and niece. In many instances two or more children have the disease whilst the parents appear to be healthy. All four affected members of the family I am reporting had apparently healthy parents. Either we must alter our clinical conception of Graves's disease altogether, and accept the most trifling departures from the normal

as evidence of its presence, or we must admit that Graves's disease itself is not hereditary. The second alternative is the more reasonable. The facts that the disease is so rarely present at birth and is so variable in its date of onset, and that it is so often transmitted by apparently healthy parents, are most easily explained by supposing that a constitutional weakness of the thyroid gland, a thyroid diathesis, rather than Graves's disease itself, is inherited. If this is accepted, the pedigrees are no longer difficult to explain on the Mendelian theory. The constitutional weakness of the gland is inherited as a dominant, and some of those who inherit it may remain apparently normal, while others may develop any or all the signs and symptoms of the disease.

This view of its ætiology is supported by the observations of Curtin in America and of Pern in Australia. Both have noticed its great frequency in certain families living in areas where endemic goitre is common, and Curtin has collected records of no less than thirty-five families in which the disease has affected brothers and sisters or parent and child. Whether it is deficiency of iodine in the soil, or infected drinking water, or both, that has a deleterious effect on the thyroid gland in these regions, there can be no doubt that something in the local conditions acts injuriously on the gland. The large number of hereditary cases in these districts is explicable on the ground that this injurious influence causes many with the diathesis to develop Graves's disease, who had they lived elsewhere would not have done so, but would have been regarded as normal individuals.

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ON PYELITIS COMPLICATED BY JAUNDICE.

BY

PROFESSOR E. GÖRTER and DR. G. O. E. LIGNAC

(From the University Clinic for Diseases of Children, and the University Laboratory for Pathology at Leyden.)

Some time ago I was interested by a suggestion in a paper in the Monatschrift für Kinderheilkunde,[1] that the peculiar yellowish tint shown by children suffering from pyelitis might be due to an hyperbilirubinæmia. In relation to this suggestion the following observations are of special interest.

CASE 1. L. N., 3½ months old, fell ill with symptoms of an acute infectious complaint: he was restless, cried day and night, had fever, with a little cough, and vomited immediately after taking food, or refused to take his bottle. Moreover he was tender when touched.

During the first five days there was nothing to be found that could be considered as the cause of the fever; but then new symptoms appeared. The colour of the child became yellow, urine was dark brown, and at the same time the stools were completely decolourized after having been fluid and dyspeptic some days before. At the same time the patient became somewhat somnolent.

The child, although prematurely born at 8 months with a birth weight of 2·5 kgrm., had developed satisfactorily and had never been ill before. Nevertheless the mother had the impression that his colour had always been yellowish, though her assertion seems doubtful and is not confirmed by her doctor. The parents were healthy, have had no other children, and no other case of jaundice could be traced in the neighbourhood. The child had been breast fed during the first month of his life, afterwards he had been fed on mixtures of cow's milk to which rather large amounts of meal and sugar had been added. He took more than one litre every day.

On examination the child appeared to be normally developed, presented a thick layer of subcutaneous fat, weighed 5·4 kgrm., but his skin was somewhat flabby on palpation. The colour of the skin was a pronounced dark yellow, like saffron; the conjunctivæ had a greenish tint. He was slightly somnolent and although his temperature was continually high, he did not give the impression of being seriously ill.

Nothing abnormal could be detected in lungs and heart. The abdomen was somewhat distended, the spleen was enlarged, palpable and rather hard. The liver was enlarged and hard on palpation. No enlargement of lymph-glands. No rickets. Urine was dark-brown, containing much bilirubin. Moreover we found albumin, many leucocytes, some red blood cells, and epithelial cells and large numbers of short Gram-negative bacilli. The stools were grayish-white, and did not contain any biliary pigment.

On bacteriological examination a pure culture of para-colon bacilli was obtained.

The blood was not examined, because we feared a serious bleeding from even a small wound, an experience we had previously encountered in a new-born infant suffering from fatal jaundice.

The condition of the child remained practically identical during the first week of its stay in the hospital. No improvement whatever was obtained by the use of urotropin or saliformin; and he lost weight, although he took fair amounts of food (buttermilk) and had no vomiting or diarrhœa. But after a few weeks his condition grew worse and worse and he died suddenly from exhaustion. There were no other symptoms observed besides those already mentioned, and we found that even during the last days no bile had passed to the intestine.

The results of the autopsy are given later in this paper.

It seems to me [E. G.], that this case ought to be considered as a coli septicæmia, in which bacilli have been excreted in the pelves and in the bileducts. and have been able to settle there, although proof is lacking of the presence of colon bacilli in the bloodstream. It is certainly a striking fact that the child had not, at the beginning, the appearance of being dangerously ill, and did not show any symptoms besides those with which we are familiar in an uncomplicated case of pyelitis. Perhaps it would be more correct to make the diagnosis of pyelitis complicated by an infectious jaundice, as we were obliged to do in two other cases which we have since observed.

Case 2. W. O., a girl, 9 months old, was sent to the hospital by her physician because she had had fever for a week.

The actual disease began ten days before admission with a chill, followed by a fever which lasted till we saw her. The child vomited several times, had no diarrhœa, but lost weight because it refused food. It cried on being touched. There were no symptoms capable of interpretation as the cause of the fever. She had suffered from measles at the age of 3 months. No other people suffering from illness could be traced in her surroundings. Although she had never been breast fed, she had developed fairly well, while under the supervision of the infant welfare centre, on ordinary 2/3 milk mixtures. She weighed 7·2 kgrm. on admission.

She was rather a fat child, having the characteristic pale and puffy face of a patient with pyelitis. No other symptoms of any importance could be found beyond the typical urinary findings : albumin, an enormous number of pus cells and colon bacilli, and from time to time some casts. The colon bacilli were atypical in so far as they did not produce indol, and did not split saccharose.

The pyelitis was treated first of all by the alkaline treatment introduced by John Thomson, This produced a rapid fall of temperature after 5–6 days. Later we tried to get rid of the persisting pyuria by auto-vaccine treatment without success in this case. It took three months before the urine was free from pus.

It is clear that this was a typical, and not very serious, pyelitis. Nevertheless we noticed on admission that the child had a slight degree of jaundice; not only the skin was yellowish, but the conjunctivæ and the scleræ were yellowish green. The blood contained more than 20 mgrm. of bilirubin per litre, being four times the normal amount. The direct reaction was negative.

Case 3. The other patient, E. G., was a girl of 6 months, who on admission on 17.4.1926 was seriously ill. Seventeen days before the child had started a fever, which had persisted. During the first few days there were no gastro-intestinal disturbances, but for the 2 or 3 days previous to admission there had been some vomiting and diarrhœa. The patient had lost considerable weight and had refused food.

The chief symptoms noticed were that she was coughing and had some dyspepsia, that she was tender to the touch, without showing any stiffness of the neck. She was quiet and somnolent. A few days ago the yellow discoloration of the skin had attracted the attention of the parents. The child was very fat, had been overfed with milk (1½ litre every day) and considerable amounts of farina. Since her illness her weight had fallen from 8 to 7·340 kgrm.

The fat pasty faced child seemed slightly toxic, and had a distinct jaundice. She had rickets. The liver was somewhat enlarged and firm in consistency. In the lungs there were signs of bronchitis, but none of consolidation. Under the left costal margin we could feel a tumour, which gave the impression that it was an enlarged kidney.

In the urine we found albumin and pus, with a great many colon bacilli—slightly atypical in character on bacteriological examination—and rare chromocytes and casts, and at the same time some bile-pigments, bilirubin as well as urobilin. The blood serum was yellow : the direct reaction of H. v. d. Bergh was positive.

It took a long time to establish a complete cure. The temperature remained high for almost a month, with only a few days of normal temperature. As was indicated by the weight curve, the child was very hydrolabile, for an injection of saline produced a quick rise in the curve.

At the end of the first month, the tumor had disappeared and there was no trace of jaundice left.

Cases Previously Reported.

Among the authors who have mentioned the occurrence of jaundice in cases of pyuria, we must cite Finkelstein[2], who writes in his book: "Eine ziemlich seltene aber um so auffälliger Komplikation bildet die Vereinigung der Pyelitis und Ikterus."

Several authors[3, 4, 5] have given descriptions of cases that were remarkable owing to some special feature, but so far as I know no autopsies have been made which throw any light on the condition of the liver. As to the clinical study of the form of the disorder of the liver, in one case reported, the bilirubin reaction of Hymans van den Bergh was found to be a *direct* one.

In the ten cases observed by Finkelstein, only one could be considered as a septicæmia, whereas in all the other cases complete cure was obtained, even sometimes in a strikingly short time, although serious symptoms were present.

Mazzeo[4] has given an account of a child of ten years old who had a pyelocystitis complicated by jaundice with great enlargement of the liver and spleen. In the urine a staphylococcus was discovered. Complete cure was obtained by auto-vaccine treatment.

Greenthal[3] saw a premature child of 7 weeks ill with a mucous and hæmorrhagic diarrhœa, who suffered afterwards from a grippe followed by pyuria.

In the case reported by W. Bayer,[6] the jaundice was probably due to the transfusion and not to the pyuria. This child after a temporary improvement died, having presented œdema and oliguria and jaundice. No autopsy was held.

On the other hand Lasch, Fischer and Silber[1] saw a series of twelve severe cases of pyelitis, of which five were fatal. All but one of the fatal group had an increase of the bilirubin in the serum, whereas none of the surviving patients showed this. They cite another group of nine infants suffering from different infectious diseases (6 pneumonia, 1 meningitis, 1 retropharyngeal abscess and pemphigus), among whom they found one only who presented a high level of bilirubin in the blood. The increase of bilirubin was pronounced; in this patient it reached 4·6 mgrm. per 100 c.cm., whereas in the others it was not above 1·3 mgrm. per cent.

Autopsy on Authors' Case.

Case 1. L. N., aged 4 months, boy, length 58 cm., and weight 5 kgrm. The skin was saffron coloured, the scleræ were also intensely yellow from jaundice. Rigor mortis was strongly developed; the hair was thin, the anterior fontanelle was almost entirely closed. Irides were grey-blue, the diameter of both pupils was 3 mm. Post-mortem staining of the tissues of the back was well developed, and could not be displaced by pressure. Both testicles were present in the scrotum; there were no signs of rickets; the external lymphatic glands were not swollen.

On internal examination it was observed that the blood-vessels in the ligamentum teres were obliterated. The subcutaneous fat was a few millimetres thick and of an intense yellow colour. The muscles were well developed, in good condition and of a red-brown colour. The liver looked dark green, the lower edge being 3 cm. below the right costal margin. The spleen was not visible. The position of the diaphragm was on both sides at the level of the 5th intercostal space. The sternum contained 5 centres of ossification.

The lungs were collapsed slightly. The pleural cavities contained no free liquid; there were 5 c.cm. of clear, yellow liquid present in the pericardium. All the serous membranes were smooth, glossy and transparent.

Heart. Weight, 40 grm. The yellow colour of the endocardium (jaundice) was remarkable. The blood in the cavities was liquid and dark violet.

Lungs. The anæmic portions of the lungs were conspicuous by their yellow colour, the bronchial mucous membrane was also of a yellowish tint and covered with mucus. The sternal and parasternal portions were emphysematous, and some patches of lung tissue in the paravertebral areas were atelectatic (on the right side more pronounced than on the left). Microscopic examination showed a catarrh of the bronchioli (mucous and leucocytic inflammation) and focal inflammations in the lung (sero-fibrinous degenerative inflammation), probably broncho pneumonia.

Glands. All the internal lymphatic glands were somewhat swollen, and of a distinct red violet colour. Microscopic examination indicated that there existed a pronounced erythrophagia. The lymph sinuses were filled with erythrocytes, which lay partly free, partly enclosed in swollen reticular cells. Morsels of erythrocytes were present here and there.

Spleen. Through the capsule the contents appeared to be of a light violet colour. Dimensions: 3 by 6½ by ½ cm., and weight 25 grm. The capsule could be slightly wrinkled. The lower pole of the spleen was of a dirty green colour (necrotic). On section a trace of blood appeared on the surface, the Malpighian bodies could just be seen; the trabeculæ were well developed. The pulp was of a light violet colour, and under pressure slightly resistant. Under the microscope it was observed that the pulp and reticular cells were swollen, and phagocytosis of erythrocytes was clearly present in the reticular cells. Some hæmorrhages were also to be seen. Groups of polymorphonuclear leucocytes were to be found in the pulp. In some places the connective tissue was increased (slightly local fibrosis). Stains for bacteria had no results. The presence of splenitis was diagnosed.

Liver, gall-bladder and large bile-ducts. The gall-bladder was not swollen; on exerting a light pressure on the gall-bladder, light brown bile appeared at the papilla of Vater, though the contents of the intestine were not coloured by bile. The bile in the gall-bladder was viscous, and light brown in colour. The wall of the gall-bladder was normal.

On section but little blood appeared on the surface of the liver, which was of a diffuse green colour, showing patches of a dark green colour. The cut surface did not extrude the capsule. Weight of the liver, 250 grm. Microscopically the portal connective tissue was infiltrated throughout by polymorphonuclear leucocytes (*cf.* Fig. 1, showing a lobule of the liver slightly magnified, and Fig. 2, an area of portal connective tissue highly magnified); further it contained distended capillaries, filled with blood. The small bile-ducts were often difficult to see in the connective tissue. Further, there were also inflammatory connective tissue cells present.

Staining for bacteria in the liver was without result. Bile pigment in the liver cells was to be found especially in the central portions of the liver lobule (*cf.* Figs. 1 and 3), and here there could be also seen large liver cells with many nuclei, clustered together (compare Fig. 3 particularly), so-called multinucleated giant liver cells (irritated liver cells). Liver cells, containing fatty vacuoles, were to be seen here and there. *Diagnosis:* Cholang(iol)itis and pericholang(iol)itis. What sort of jaundice was present here, is difficult to determine.

Suprarenal bodies consisted of violet medulla and grey cortex. Microscopically, hæmorrhages appeared to be present in the medulla.

Kidneys were large (weight, 125 grm.). On section the tissue bulged above the capsule and was anæmic. Mucous, yellow matter was present in the pelvis; thin, yellow membrane covered the pyramids and the mucous membrane of the calyces. Microscopically these membranes consisted of fibrin and desquamated surface-epithelium (*cf.* Fig. 4, portion of a calyx slightly

magnified). The vessels in the mucous membrane of the pelvis were distended and therefore better seen. The colour of the cortex of the kidney was greyish yellow, yellow patches being present here and there, while fan-shaped yellow lines stretched from the tips of the pyramids to the edge of the medulla.

Microscopic examination showed that fibrin was present on the epithelium of the pelvis, even extending here and there between the epithelium cells. The hæmoglobin gave the fibrin a glittering light brown colour (*cf.* Fig 4). Polymorphonuclear leucocytes were also found in patches between the epithelial cells, while the sub-epithelial connective tissue was œdematous and contained here and there infiltrations of lymphocytes and polymorphonuclear leucocytes. The capillaries were also distended and filled with blood. The tubuli recti in the medulla were in some places wider than normal and filled with a homogeneous or granulated matter, coloured pink by eosin and full of polymorphonuclear leucocytes (*cf.* Fig 5, portion of medulla highly magnified). Colonies of bacteria were present, some between, and some in, the tubuli recti. These colonies consisted of bacilli which were Gram-negative (*cf.* Fig. 5.) The capillaries between the tubuli recti were distended and filled with blood, there were also red blood corpuscles scattered outside the blood-vessels.

The yellow patches in the cortex near the edge of the medulla consisted of polymorphonuclear leucocytes with pycnotic nuclei, while the kidney tissue at that place was scarcely recognizable as such (commencement of pus-formation). No particular changes were to be seen on the Malpighian bodies; the protoplasm of the tubuli contorti in general showed granular degeneration, the nuclei were badly coloured.

Bladder. The mucous membrane was of a yellow colour (jaundice). Microscopically there was hardly any trace of inflammation.

Aorta. The intima was of a yellow colour (jaundice).

Intestine. Pathologically nothing special was noted.

Pathologically a diagnosis of fibrinous pyelitis and cellular pyelo-nephritis was reached.

Conclusion.

The post-mortem investigation permits us to formulate the following conception of the disease in this four month's old boy :—

Both kidneys, infected by Gram-negative bacilli (in connection with the clinical-bacteriological investigation, they belong to the bacillus coli communis group), and showing signs of pyelo-nephritis, are the centre of the disease. The infection has been of a serious nature, not only by reason of the nature of the tissue changes in the pelvis (fibrinous pyelitis) and in medulla and cortex of the kidney (cellular to suppurative nephritis), but also because of the presence of cholang(iol)itis and pericholang(iol)itis with icterus and splenitis.

It is difficult, from this post-mortem investigation alone, to be dogmatic about the pathogenesis of this disease. We can only ponder on certain possibilities :

1. Has it been a coli septicæmia with particular localizations in the pelves of the kidneys and in the liver and spleen ?

2. Have the pyelitis and pyelo-nephritis first arisen by infection by way of the blood-vessels, and subsequent coli infection localized in the liver and spleen ?

3. Has the pelvis been infected with colon bacilli by the lymphatics from the intestine[7, 8], so that a pyelitis has developed with all its consequences ?

It may be recalled that on section the lower urinary organs were almost entirely free from inflammation.

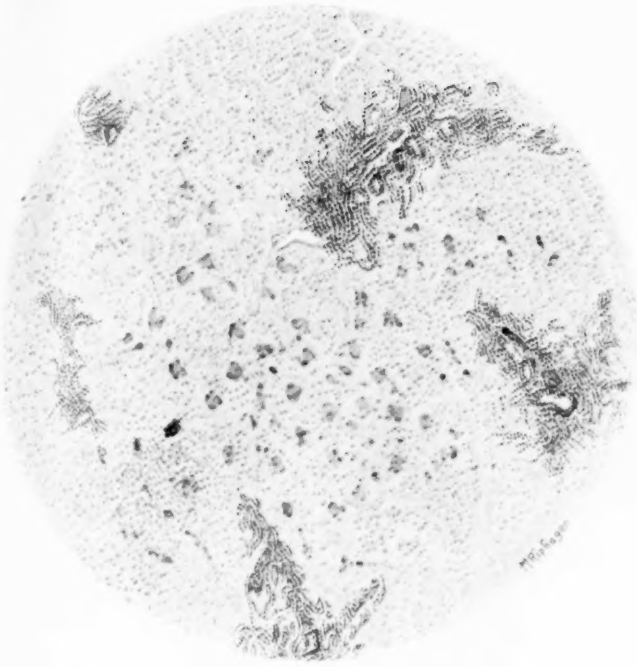

Fig. 1.—Slight magnification of a liver lobule showing cellular cholang(iol)itis, pericholang(iol)itis. Bile pigment in the central portions of the liver lobule.

Fig. 2 —High magnification of an area of the portal connective tissue showing cellular inflammation.

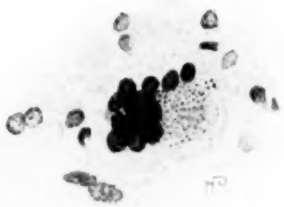

Fig. 3.—Giant liver cell with many nuclei and bile pigment.

Fig. 4.—Fibrinous pyelitis (slight magnification).

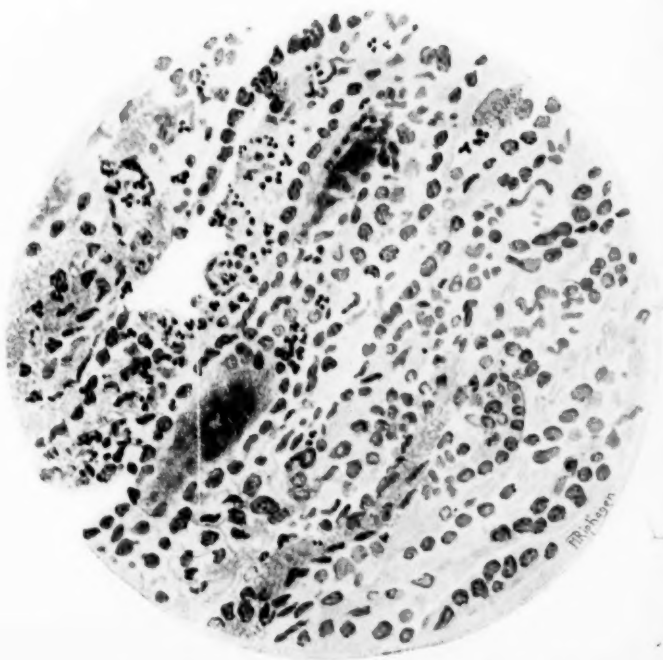

Fig. 5.—Cellular inflammation of the medulla (tubuli recti) and two colonies of bacteria (finely granulated, blue stained patches).

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A CASE OF PARATYPHOID B. INFECTION WITH PURPURA AND SPECIFIC BRONCHO-PNEUMONIA.

BY

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and

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The recent epidemic of paratyphoid fever in London has sent several children suffering from the disease to this hospital. One case was so remarkable, and so rapidly fatal after admission, that it deserves record, especially since the bacteriology of the various lesions was clearly established.

A good history from the parents, details from the family doctor, with charts from the local hospital, made a full account of the early stages possible and reasonably accurate.

Frances P., aged 8 years, became ill on July 15th, 1928, complained of headache, and vomited once or twice. Until that day she had been quite well, and had been helping with the hay harvest. Next day her bowels were opened several times; loose motions were passed, but no blood. On July 17th her doctor was called, who found a high temperature, but no other physical signs.

A week later two or three red spots were noticed on the abdomen, and the temperature fell, to rise again the same day. The patient's condition was much improved and on the 25th and 26th she was dressed and brought downstairs, but not allowed to walk about.

On the strength of a Widal reaction positive to B. paratyphosus B. on July 28th, the child was taken to a local hospital. The same evening her temperature rose to 104°, remained there for eight hours, and was reduced by sponging. The pulse rate at this time was only 104 per min. After falling to normal, the temperature became remittent at about 100°, and rose slowly during the next six days to 101·5°. On July 30th small purpuric patches were noticed on the lips and neck; then an echymosis into one conjunctiva, and a day or two later patches of purpura appeared on the trunk. Hæmaturia followed closely on the appearance of skin hæmorrhages, and on Aug. 4th and 5th the patient vomited blood. The pulse rate which was 70 to 84 per min. until the evening of Aug. 1st, began to rise and was soon varying between 100 and 120 per min.

Aug. 5th. Patient was admitted to the Hospital for Sick Children, Great Ormond Street. She was blanched, and so ill that no detailed examination was made. Purpuric patches and petechiæ were scattered irregularly on the face, neck, and chest; a clot disfigured the left conjunctiva, and a bruise showed faintly over the left ankle.

An hour after admission 250 c.cm. of whole blood, from the father, were given into the left median basilic vein, and later Hæmoplastin was injected intramuscularly.

The pulse rate rose after this operation, but its volume was increased, and the colour of the patient's lips and cheeks improved.

Aug. 6th. Pyrexia and vomiting continued. In the evening the patient cried out as if in abdominal pain, became very restless and vomited an ounce and a half of thick tarry fluid on the edge of which was a little bright red blood. Morphia was given. The pulse rate rose during the day to 152 per min. and the respiratory rate was steady at 28 per min.

Aug. 7th and 8th. During the next two days the patient seemed to hold her own. She vomited twice only, and the pulse though rapid was of fair volume. During this time the respiratory rate rose from 28 to 44 per min., and the patient was only semi-conscious. A blood culture and Widal test were made and the blood cells and platelets counted.

Aug. 9th. During the 9th extreme restlessness and noisy delirium exhausted the child, but at 10.30 p.m. she had a fair pulse, at 160 per min. Her temperature was 101°. An hour later she was seen in a state of acute heart failure. She was comatose, the radial pulse had vanished, and there was increasing pulmonary œdema : in an hour she was dead.

Laboratory Examinations.

Five cubic centimetres of blood were taken on Aug. 7th when the patient's temperature was 103°. Cultures of this in broth, and enriched broth media remained sterile after four days' inoculation at 37°C. A Widal test on the same day showed agglutinations of B. paratyphosus B. up to a dilution of 1 : 50,000. At the same time the blood showed a marked thrombocytopenia ; the platelets numbering 20,000 per c.cm., and the red cells 3,000,000 per c.cm.

On the following day a blood count showed only 2,200,000 red and 20,000 white cells Among these were 51% polymorphs, 31% lymphocytes, 5% myelocytes, and 9% transitional cells. Nucleated red cells were present to the extent of sixteen per hundred white cells. The child's grave condition prevented the repetition of these investigations.

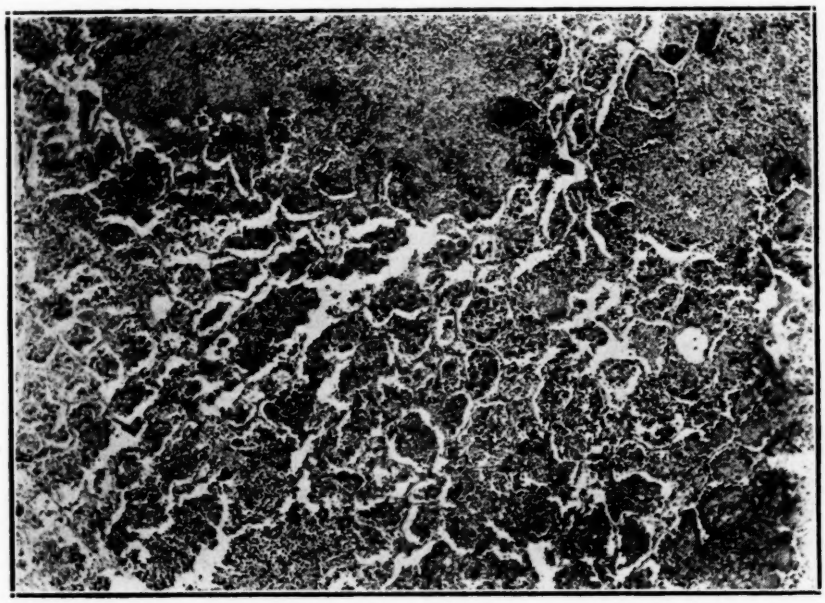

Fig. 1. Micro-section of Pneumonic Lung.
($\frac{3}{4}$ obj.)

Post-mortem Examination.

A post-mortem examination was made by Dr. Monerieff. The most striking feature was a suppurating pneumonia almost confined to one lobe. There were punctate hæmorrhages all over the pleuræ, and the right pleural cavity contained 1½ oz. of pus. The upper lobe of the right lung was covered with purulent exudate, was solid, and showed bright orange yellow patches on section. At the apex of the left lower lobe was a similar patch with surrounding consolidation.

Microscopic sections of the lung (see Figure 1) showed exudate into the air cells with lymphatic engorgement and cellular infiltration in the interstitial tissue. Patches of necrotic lung lay next to this broncho-pneumonia, and appeared stained only by the acid dye, amorphous in structure, or containing the ghosts of alveoli,

The mediastinal glands were slightly enlarged; there was no evidence of tuberculosis. Punctate hæmorrhages covered the pericardium and brain and were scattered over the intestines. The most extensive sub-peritoneal hæmorrhage was in the left iliac fossa which was dark with blood. The intestines showed no enlargement of Peyers patches and no ulcers in the small gut. In the large bowel several solitary follicles were enlarged, and one or two were beginning to break down. The mesenteric glands were not enlarged. The spleen weighed 50 grm., and was soft: the liver weighed 700 grm., and showed extensive fatty degeneration.

Bacteriology.

When discovered, the empyema pus was contaminated, but swabs were taken from the broncho-pneumonic lung, and from a large mediastinal gland. From each B. coli and non-lactose-fermenting organisms were grown. The latter when isolated, gave sugar reactions typical of B. paratyphosus B. Milk was turned slightly acid, but did not later become alkaline. These organisms were agglutinated strongly by the standard agglutinins sera for paratyphoid B. of the Medical Research Council. This was taken as evidence that the pneumonia was specific and due to B. paratyphosus B.

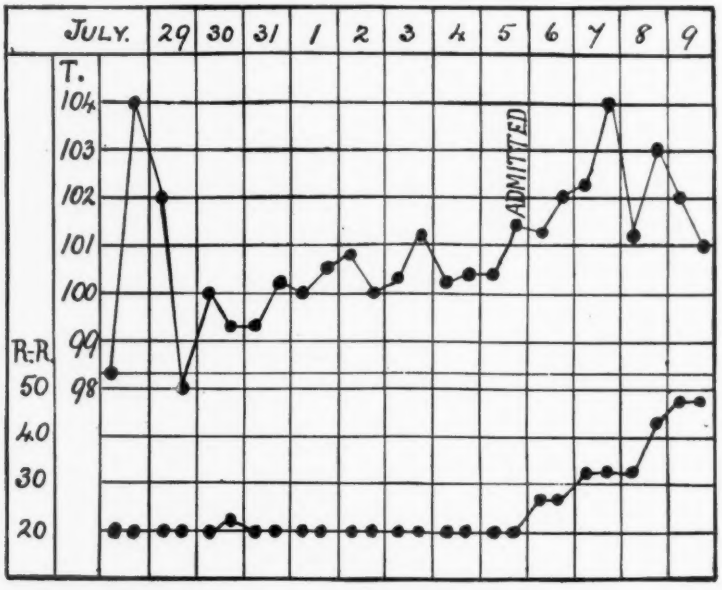

Fig. 2. CHART SHOWING TEMPERATURE AND RESPIRATION RATE.

The interesting points in the laboratory and pathological findings are :—

1. The extent of suppuration in the lung lesions, and the recovery of specific organisms from the lungs and mediastinal glands.
2. The leucocytosis of 20,000 per c.cm. where a leucopenia and relative lymphocytosis were to be expected. This must have been the result of reaction to suppuration in the lung.
3. The extremely high titre of agglutination in the patient's blood in the short time (three weeks) from the commencement of the illness. This indicates a good response by the production of specific anti-bodies.
4. The almost complete absence of any intestinal lesions although this is supposed to be the portal of entry of the infection.

Discussion.

Pneumonia is apparently a common complication of fatal cases of paratyphoid infection. In 1915 Lord Dawson[1] described four instances in fifteen autopsies on adults. In one of these there was cavitation with broncho-pneumonia, but this had not the bright orange appearance of the suppurating lung we found. Stolkind[2] noted broncho-pneumonia in eight out of eleven autopsies, and the recovery of the organism from the blood in a large proportion of these cases emphasized the septicæmic nature of the disease. The occurrence of this complication was reviewed in 1921 by Pincsohn[3] who quoted cases of paratyphoid A with specific pneumonia, infarcts and hæmoptysis. Pneumonia appears to be commoner in paratyphoid A than in paratyphoid B. Lemière[4] and Loeper[5] in the next year each quoted a case of paratyphoid B. septicæmia with lobar pneumonia. Both cases recovered. The lung suppuration we describe may be allied to such complications as osteitis and purulent thyroiditis that have been described by various authors. It is possible that in the present case the brunt of a paratyphoid septicæmia fell upon the lungs, and that, when these broke down with formation of abscesses, the systemic circulation was further infected with a massive and fatal dose of micro-organisms.

In 1907, Keany[6] shewed a case of typhoid fever complicated by purpura. Vincent and Muratet[7] mention that purpura may occur during typhoid, and express the opinion that its presence always makes the prognosis grave. Roubier and Brette[8] in 1919 emphasized the rarity of this complication. They made a distinction between a 'heralding purpura' and one which occurs during defervescence or convalescence. Of this '*purpura tardif*' they recorded two cases in adults. In both purpura appeared after the temperature had fallen, was confined to the lower limbs, and in one case it was associated with hæmaturia. Both cases recovered, and the authors gave it as their opinion that this late purpura is the less dangerous, in spite of the fact that several fatal cases had at that time been recorded. In a discussion on paratyphoid infections at the Royal Society of Medicine in 1916[1] purpura was not mentioned, and in 1918 Stolkind[2] reviewed all the literature of paratyphoid in children without referring to this complication. A case was recorded by Trabaud[9] in 1923 of an adult male with paratyphoid A. and jaundice, in whom defervescence was complicated by a purpuric and erythematous eruption all over the body, accompanied and followed by a right lower lobar pneumonia. The patient recovered, the jaundice being the last sign to disappear. Gwosz[10] in 1927 reported general purpura, with bleeding gums, epistaxis and melæna in a child of five years, on the twenty-first day of paratyphoid B. fever. The hæmorrhages increased and two days later hæmaturia appeared. Argoflavine was given intravenously; no further hæmorrhages appeared after the 25th day and the patient recovered. This case showed a progressive leucopenia to 4,900 white cells with eosinophilia on the 23rd day of the illness. The count rose to 7,400 on the 26th day as the hæmorrhages decreased. At the onset of the purpura there was marked thrombocytopenia, the platelets being only

100,000 per c.mm. They rose to 264,000 on the 34th day of the illness. The author admits that in view of previous cases the recovery in this case was an unusual termination and attributes it to the administration of argoflavine.

Many authors stress the variability of intestinal lesions. Two of Lord Dawson's cases (1916) showed none, and in one case lesions were confined to the large bowel. In two only of Stolkind's eleven cases was there severe folli cular enteritis. Holwede[11] reports one autopsy at eight months, at which a bilateral pulmonary consolidation with empyema, was found. Ulceration was almost entirely confined to the large intestine.

During the last twenty years at the Hospital for Sick Children, there have been only two autopsies on proved cases of paratyphoid B. and one on a case of paratyphoid C. infection.

The first (1915) in a child of 11 years, showed no enlargement of Peyers patches, but swelling of the solitary follicles was present, without enlargement of the mesenteric glands. Broncho-pneumonia and empyema were present.

The second (1921) in a baby aged six months, showed catarrhal inflammation of the large bowel only. B. paratyphosus B. had been grown from the stools, and the illness had lasted six weeks.

The third (1927) in a baby aged six weeks, showed an abscess in the right humerus from which B. paratyphosus C. was isolated. There were no intestinal lesions.

It would be of interest to discover why some of these apparently typical cases of paratyphoid infection should suddenly develop purpura. Vincent and Muratet say that the platelet count is always low in typhoid and may be only 50 per 100,000 red cells. Damage to the cardiovascular system by toxins, and an extreme deficiency in certain components of the blood, may each occur in this disease. The relative importance of these phenomena in the causation of purpura remains uncertain. It is possible that even in association they are only predisposing causes.

In the case that we report, an early infection of the lungs may have been followed by a massive systemic infection, of which the purpura was merely a toxic manifestation. If the records of the respiratory rate (Fig. 2) are accurate, however, it seems likely that extensive lung damage did not occur until late in the disease.

We are indebted to Dr. H. Thursfield for the opportunity of reporting this case.

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OBSERVATIONS ON THE CHLORIDE, SUGAR, AND CALCIUM CONTENTS OF THE CEREBRO-SPINAL FLUID IN CHILDREN.

BY

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Examination of the cerebro-spinal fluid by the bio-chemical method is a relatively recent means of approach towards elucidation of accurate diagnosis, yet much has been written in support of, and against, its reliability. With the elaboration of more accurate methods it is, however, clear that an increasing value can be placed on the results obtained by this means.

The importance of any aid in differentiating the causes of the meningeal syndrome, which appears so frequently in children, is self-evident. The interpretation of bio-chemical results often requires more consideration in children than in adults. Thus the range of " normality " is greater in the child ; probably the result of its more unstable organization. This point is well brought out by Donald Stewart[1] in his paper on the normal cerebro-spinal fluid in children of various ages.

It is our intention in this paper to record some observations on the cerebro-spinal fluid in sick children under the age of 12 years. We have considered more especially the chloride, sugar, and calcium contents of this fluid.

I.—Chloride Content.

(*a*) *In Non-meningitic Cases.*

The chloride content of cerebro-spinal fluid has been estimated in non-meningitic cases, in children showing meningismus and in various forms of meningitis (Tables I-VI).

Table I shows the chloride content of the cerebro-spinal fluid as obtained by lumbar puncture in children who were suffering from some symptoms referable to the nervous system, but in none of whom was there any clinical or other evidence of inflammatory or other involvement of the meninges. The readings show a maximal and minimal figure of 783 and 696 mgrm. per cent. respectively, with a mean of 730 (Chart I).

No opportunity has been afforded us to carry out observations on healthy children, but it is of interest to compare these findings with Stewart's normal series. His figures show a considerable range in the chlorides, namely, 630 to 760 mgrm. per cent., with a mean of 728, a value almost identical with that

TABLE 1. CHLORIDE CONTENT IN CERTAIN NON-MENINGITIC CASES.

Case.	Age.	Diagnosis.	Chlorides.
			mgrm. p.c.
J.S.	9	Uræmia	755
J.B.	9	Nephritis	719
G.A.	10/12	Hydrocephalus	703
B.W.	3/12	Cerebellar Tumour	713
H.O.	2	Hydrocephalus	709
B.W.	3/12	Cerebellar Tumour	727
I.C.	1	Pink Disease	705
J.E.	5	Cerebral Tumour	696
J.C.	2	Cerebral Tumour	710
E.P.	6	Cerebral Tumour	725
J.A.	5	Cerebellar Tumour	749
I.B.	4	Pontine Tumour	763
I.B.	4	Pontine Tumour	700
D.P.	10	Encephalitis	757
B.C.	11	Encephalitis	736
B.C.	11	Encephalitis	737
H.C.	11	Encephalitis	776
B.S.	2½	Polio-encephalitis	740
E.H.	4	Polio-encephalitis	704
E.H.	4	Polio-encephalitis	732
W.H.	6	Encephalitis Lethargica	715
D.C.	4/12	Encephalitis	741
D.C.	4/12	Encephalitis	711
F.S.	9/12	Meningismus	725
K.P.	2	Meningismus	730
L.M.	7	Meningismus	703
L.M.	7	Meningismus	720
J.S.	6	Mental Deficiency	740
W.D.	9/12	Mental Deficiency	783
M.G.	—	Epilepsy	769
M.K.	—	Convulsions	748
F.P.	3	Cerebellar Tumour	755
B.	6/12	Measles, Convulsions	711
E.M.	6	Epilepsy	725
B.	1⅓	Convulsions	714
D.M.	2	Convulsions	738
D.C.	3	Post-encephalitis	752
D.C.	3	Post-encephalitis	730
B.S.	—	Convulsions	735
R.M.	2	Cerebral Tumour	747
J.B.	5/52	Birth Injury	703

Average = 730.

obtained by us. Caffey, Maclean and Sullivan[2] reported figures ranging from 675 to 750 in a series of normal children. We may therefore conclude, so far as our observations go, that these patients show no departure from the normal, the wide range being maintained. Further, from observations made on several of these patients it was found that, after a few days interval, a variation up to 40 mgrm. per cent. might occur in the same individual, this being in all probability related to changes in the blood chloride (vide infra).

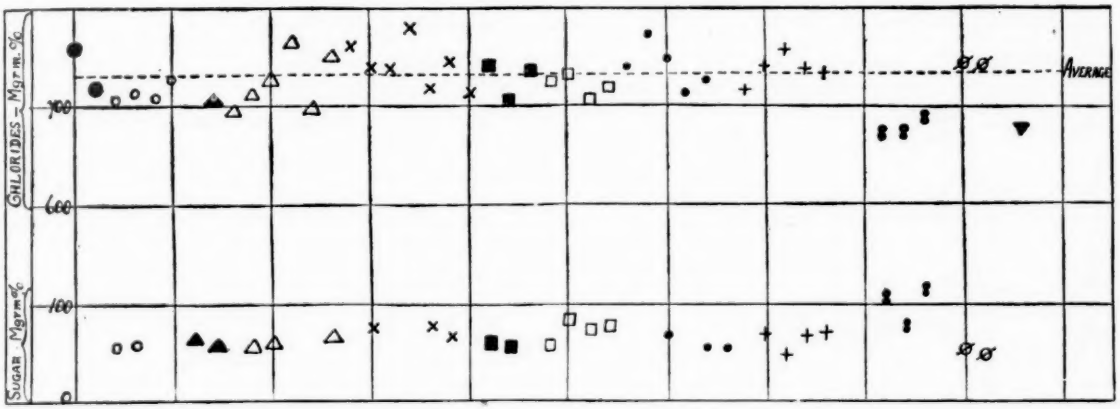
(*b*) *In Meningismus.*

Table 2a shows the chloride content in the cerebro-spinal fluid in cases of pneumonia, during the febrile period of the illness. In each instance the chlorides are below 700 mgrm. per cent. This table should be contrasted with

CHART I.

NON-MENINGITIC CEREBRO-SPINAL FLUIDS IN CHILDREN.

CHLORIDES AND SUGARS.



- Nephritis.
- Hydrocephalus.
- Acrodynia.
- Cerebral Tumour.
- Encephalitis Lethargica.
- Polio-encephalitis.
- Meningismus.
- Convulsions and M.D.
- No abnormality detected.
- Lobar pneumonia.
- Secondary Broncho-pneumonia
- Primary Broncho-pneumonia.

Table 2b which gives the results obtained in cases showing meningismus but without any evidence of pneumococcal infection. In this group all the findings are above 700 mgrm. per cent. In view of the known disturbance of the body chlorides in acute pneumococcal disease it is of interest to note the lowering of the cerebro-spinal fluid chloride in this infection.

In none of the cases was there any abnormal cellular or bacterial content, and in the case of B.H. necropsy showed a complete absence of meningitis.

TABLES 2A & 2B. CHLORIDE CONTENT IN MENINGISMUS.

Case.	Age.	Diagnosis.	Chlorides.
A.			mgrm. p.c.
B.H.	6/12	Primary Broncho-pneumonia	674
S.S.	4	Lobar Pneumonia..	670
H.S.	9	Lobar Pneumonia..	687
S.S.	4	Lobar Pneumonia..	673
N.T.	7	Lobar Pneumonia..	665
B.			
F.S.	9/12	Simple otitis media	725
K.P.	2	Adenitis	720
D.G.	4	No definite disease	747
L.M.	7	No definite disease	720

TABLE 3. CHLORIDE CONTENT IN TUBERCULOUS MENINGITIS.

Case.	Age.	Diagnosis.	Chlorides.
			mgrm. p.c.
C.L.	3	Tuberculous Meningitis	653
G.C.	?	,,	651
D.L.	8	,,	633
A.C.	?	,,	601
K.A.	8/12	,,	631
J.R.	7/12	,,	564
S.T.	1¾	,,	634
P.	?	,,	544
E.C.	10	,,	673
R.S.	8	,,	632
K.M.	1¼	,,	552
P.L.	1¼	,,	500
F.J.	4/12	,,	642
A.S.	9/12	,,	698
P.W.	1½	,,	650
M.G.	7/12	,,	556
D.M.	1⅛	,,	596
H.A.	1⅛	,,	673
T.G.	3	,,	663
L.C.	6/12	,,	647
I.B.	8/52	,,	598
K.W.	2	,,	720
M.C.	2	,,	615
K.C.	1	,,	638
A.C.	7	,,	566
			Average = 613.

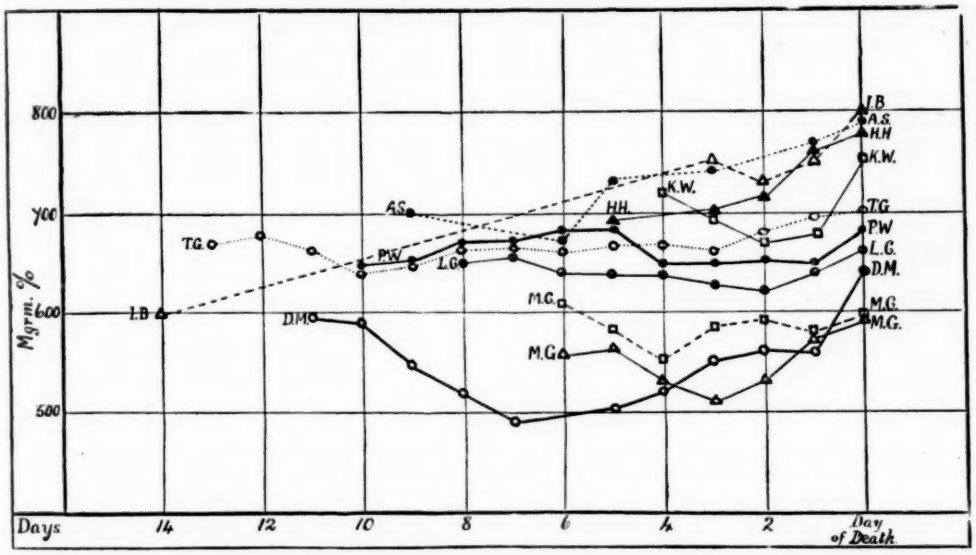
(c) *In Tuberculous Meningitis.*

Table 3 shows the chloride content of the cerebro-spinal fluid in specimens obtained on admission of the children into the hospital. The readings range from a maximum of 673 to a minimum of 500 mgm. per cent., thus giving a mean of 613 mgm. per cent., but two cases (A. S. and K. W.) show unusually high figures. These findings, it should be stressed, give the condition directly after admission of the child to hospital and are not related to the stage of the illness. Some months ago we had an opportunity to examine specimens of cerebro-spinal fluid during the course of a case of tuberculous meningitis. On plotting out a curve of the results obtained it was seen that a descent occurred in the earlier stages of the disease and an ascent in the later stages. Similar observations have since been made in ten other cases. The diagnosis in each of the cases studied was confirmed at necropsy. The results are shown in Chart II. Each curve shows a different level on the Chart, but the type of curve is the same in all cases and is uninfluenced by the course of the illness, whether this be a rapid or relatively slow one. The maximum figure on the Chart is 802 and the minimum is 493 : the former being a reading obtained in a case in the terminal stage of the illness, and the latter an earlier phase in another case. As a result of single observations in cases of meningitis, various workers have stated that the chloride in cerebro-spinal fluid in tuberculous meningitis is invariably at a low level. This statement is incorrect. Thus some of our cases (e.g., A. S., K. W., and H. H.) have readings, taken throughout the illness, within normal levels. The results we have obtained show,

CHART II.

TUBERCULOUS MENINGITIS IN CHILDREN.

CHLORIDE CURVES PLOTTED BACKWARDS FROM DEATH POINT.



therefore, that although it is common to obtain a subnormal chloride figure in tuberculous meningitis, this is not always the case, and also that it is necessary to take into account the stage of the illness.

TABLE 4. CHLORIDE CONTENT IN PNEUMOCOCCAL MENINGITIS.

Case.	Age.	Diagnosis.	Chlorides.
			mgrm. p.c
A.P.	6/12	Pneumococcal Meningitis	634
E.S.	6/12	,, ,, ...	655
K.P.	9	,, ,, ...	634
D.M.	11/12	,, ,, ...	685
T.C.	6/12	,, ,, ...	677
K.R.	8	,, ,, ...	686
B.D.	11/12	,, ,, ...	677

Average = 664.

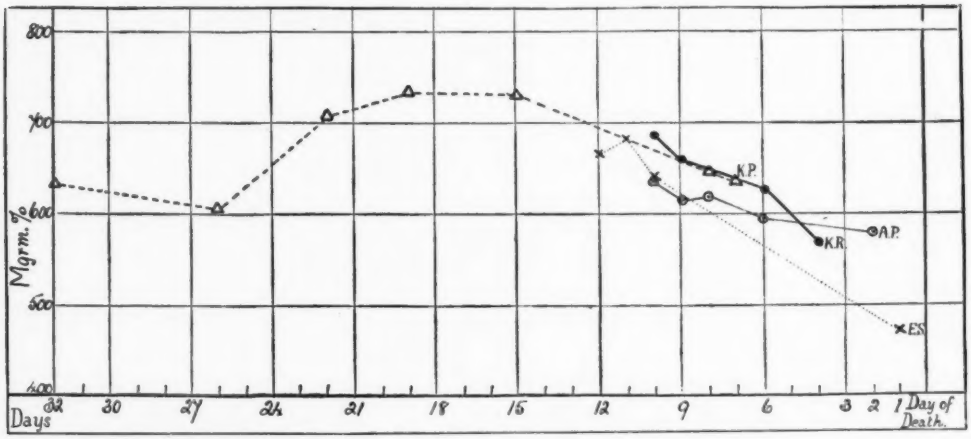
(*d*) *In Pneumococcal Meningitis.*

This series of single observations, taken on admission of the patient to hospital, shows a comparatively low reading, although not so low as the average of the tuberculous cases.

Plotting the results of examinations (Chart III) made during the course of the illness, shows a fairly characteristic curve, there being, with one exceptional case, a continuous descent until the fatal issue. The exception was obtained from a patient (K. P.) who showed unusual clinical features and a correspondingly interesting curve. On admission he presented the typical appearance of meningitis and had a slightly purulent cerebro-spinal fluid. Several days later a remarkable improvement in his general condition occurred

CHART III.

PNEUMOCOCCAL MENINGITIS IN CHILDREN.
CHLORIDE CURVES PLOTTED BACKWARDS FROM DEATH POINT.



and the cerebro-spinal fluid pressure decreased. Synchronously with this the cerebro-spinal fluid became almost clear and the chloride (and sugar) content showed a rise towards the normal limit. This state of affairs continued for nine days, when a sudden relapse occurred with the reappearance of a purulent cerebro-spinal fluid, there being also a fall in the chloride corresponding with the grave condition. The fluid became increasingly purulent and the chloride content continued to diminish until the patient died.

The average of readings obtained in the final specimens in the cases of pneumococcal meningitis is 557, a figure much lower than that found in the final specimens in tuberculous meningitis, which was 692. This is interesting since it is the opposite of that found for the average of readings of the earliest specimens.

TABLE 5. CHLORIDE CONTENT IN MENINGOCOCCAL MENINGITIS.

Case.	Age.	Diagnosis.	Chlorides.
			mgrm. p.c.
J.H.	10	Meningococcal Meningitis	644
M.B.	11/12	,, ,, ...	706
M.G.	2½	,, ,, ...	657
A.C.	4/12	,, ,, ...	615
C.W.	3/12	,, ,, ...	689
B.D.	11/12	,, ,, ...	677
		Average = 664.	

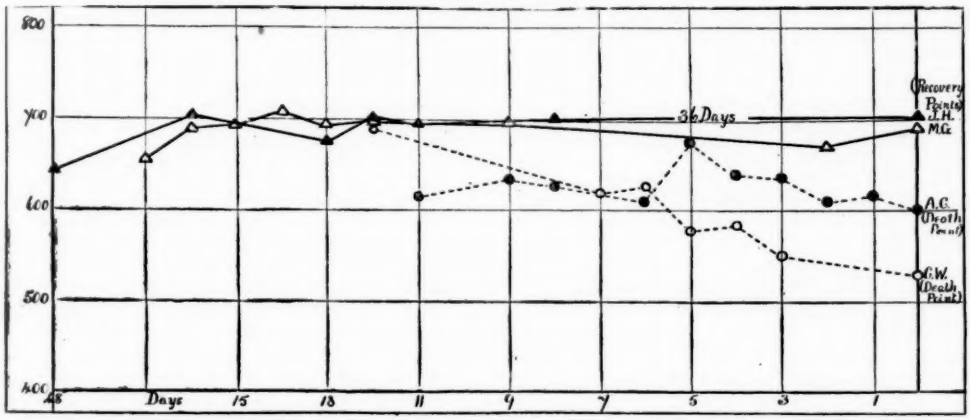
(e) *In Meningococcal Meningitis.*

Single observations made when the patients were first admitted to hospital (Table 5) show a fairly considerable variation, with a subnormal mean. Curves of serial examinations indicate, however, that the figures must be correlated with the stage of the illness and the progress of the case. Chart IV shows curves in two children (J. H. and M. G.) who recovered and in two (A. C. and C. W.)

CHART IV.

MENINGOCOCCAL MENINGITIS IN CHILDREN.

CHLORIDES.



who died. The former show a steady rise towards normal; the latter a steady fall as the case approaches an end, giving a terminal mean of 696 in the recovered and 564 in the fatal cases.

Chloride in Cerebro-spinal Fluid and Blood.

Linder and Carmichael [3] have suggested that the fall in the chloride of the cerebro-spinal fluid is dependent upon a similar decrease in the chloride in the blood, and that the relative concentration of chloride in the two fluids always remains the same. We have therefore estimated the chloride in specimens of blood and cerebro-spinal fluid taken simultaneously. The results, when more than one estimation was made during the course of the case are shown in Table 6; and Chart V shows the results in 26 cases in which only one estimation of each was performed. In all instances the chloride was estimated in the whole blood.

CHART V.

CHART SHOWING RELATIONSHIP OF C.S. FLUID AND BLOOD CHLORIDES.

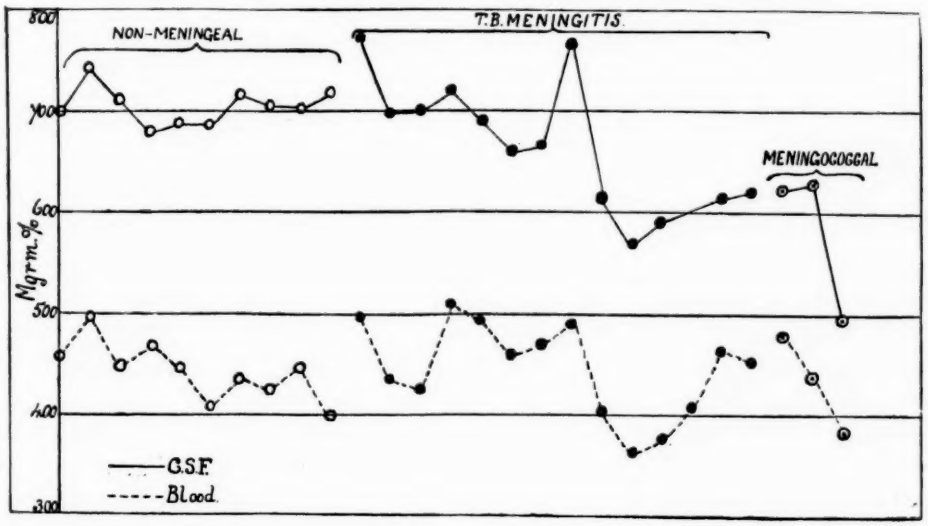


TABLE 6. CHLORIDE IN CEREBRO-SPINAL FLUID AND BLOOD.

Case.	Age.	Diagnosis.	Chlorides, mgrm. per cent.	
			C.S.F.	Blood.
D.C.	4/12	Encephalitis Lethargica	741	495
,,	,,	,, ,, ...	711	443
,,	,,	,, ,, ...	678	467
,,	,,	,, ,, ...	687	443
H.S.	9	Pneumonia and Meningismus	687	408
,,	,,	,, ,, ...	718	433
K.W.	2	Tuberculous Meningitis	720	510
,,	,,	,, ,, ...	689	492
,,	,,	,, ,, ...	660	457
,,	,,	,, ,, ...	664	467
,,	,,	,, ,, ...	763	488
M.C.	2	,, ,, ...	615	401
,,	,,	,, ,, ...	569	359
,,	,,	,, ,, ...	589	373
C.W.	,,	,, ,, ...	620	476
,,	,,	,, ,, ...	626	436
,,	,,	,, ,, ...	489	380

The Charts show that when both fluids are examined at the same time there is a general agreement between their relative chloride contents, but no strict ratio could be established. This agreement is manifest both in children suffering from meningitis and in those in which meningitis is not present, and indeed, so far as our figures go, appears to be more in evidence in the meningitic cases.

II.—SUGAR CONTENT.

(*a*) *In Non-Meningitic Cases.*

As in the chloride studies, it has not been possible to carry out a series of observations on healthy children, but the cerebro-spinal fluid sugar was estimated in a number of children who showed no evidence of meningitis. The results are sent forth in Table 7 and in Chart I.

Table 7 shows the findings in 24 cases. The cellular content was in each case normal. Stewart's series of normal children gives an extreme range of 27 to 84 mgrm. per cent., but the majority showed a figure between 45 and 70. It will be seen that our results, as in the chloride series, show a close resemblance to those obtained by Stewart.

(*b*) *In Tuberculous Meningitis.*

The estimations of the sugar content, like those of the chlorides, have been made on fresh specimens of cerebro-spinal fluid obtained serially during the course of the disease, and the findings are shown in Chart VI.

In most instances a curve having somewhat similar features to the chloride curve is obtained, in other words an early fall followed later by a rise. The maximum and minimum range is 72 and 0 respectively. It is noteworthy that in one patient (K. W.) a total absence of sugar occurred throughout the period of observation, and in four cases zero point was reached at one stage of the illness.

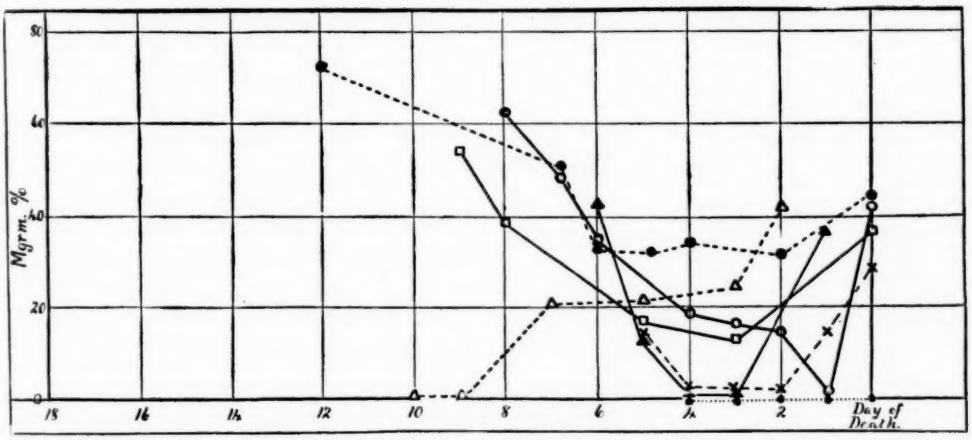
TABLE 7. SUGAR CONTENT OF CEREBRO-SPINAL FLUID.

Case.	Age.	Diagnosis.	Sugar.
			mgrm. p.c.
G.A.	10/12	Hydrocephalus	52
B.W.	3/12	„	55
R.F.	10/12	Pink Disease	63
I.C.	1	„	55
J.C.	2	Cerebral Tumour	54
E.P.	6	„ „	55
G.A.	3	Cerebellar Tumour	83
R.M.	2	Cerebral Tumour	63
V.C.	11	Encephalitis	73
W.H.	6	„	73
P.S.	2½	Polio-encephalitis	59
E.H.	4	„ „	53
D.C.	4/12	Encephalitis	63
F.S.	9/12	Simple Meningismus	59
R.P.	2	„ „	83
L.M.	7	„ „	73
L.M.	7	„ „	78
W.D.	9/12	Mental Deficiency	52
M.K.	—	Convulsions	67
E.M.	—	„	55
D.M.	2	„	67
B.S.	—	„	67
D.C.	3	Post-encephalitis	45
D.C.	3	„ „	71

Average = 63 (83—45)

CHART VI.

TUBERCULOUS MENINGITIS IN CHILDREN.
SUGAR CURVES PLOTTED BACKWARDS FROM DEATH POINT.



The results once more demonstrate that the wide range in the readings must be correlated with the particular case and with the stage of the illness, and that a fallacy may arise in making a diagnosis from a single reading.

(*c*) *In Meningococcal Meningitis.*

Four cases, two being fatal, were investigated, and the results are shown in graph form (Chart VII).

The cases which recovered showed an initial low reading, with some fluctuation from day to day until the stage of recovery was reached, when an elevation of the sugar content to the normal occurred. In neither case was zero point reached. On the other hand in each of the two fatal cases the sugar content fell to zero and remained low throughout the illness, but of these, one showed a slight rise in the moribund phase.

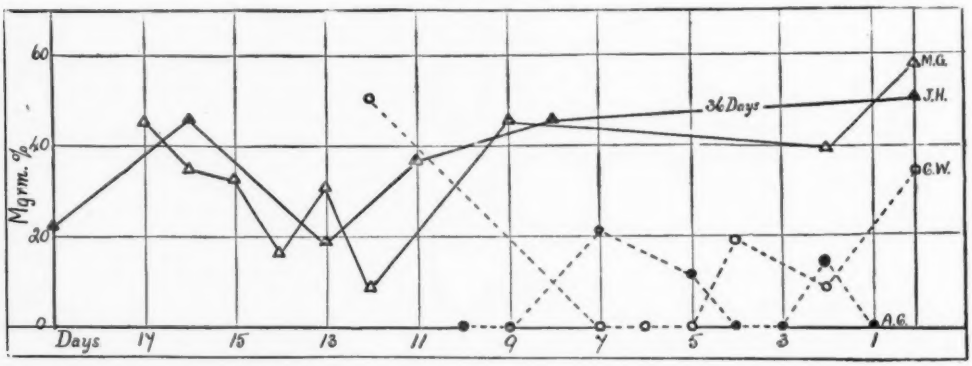
Caffey, Maclean and Sullivan[2] also found that in children recovery occurred with the return of the sugar content in the cerebro-spinal fluid to normal. This improvement might, however, be delayed for fourteen days. They showed that in uncomplicated cases anti-serum itself did not cause any rise in the cerebro-spinal fluid sugar.

Occasionally, in fatal cases, a terminal increase in the cerebro-spinal fluid sugar is associated with terminal hyperglycæmia and glycosuria.

CHART VII.

MENINGOCOCCAL MENINGITIS IN CHILDREN.

SUGARS.



M.G. and J.H. recovered. C.W. and A.C. died.

(*d*) *In Pneumococcal Meningitis.*

Four cases of this variety of meningitis were also investigated. All show low readings and in one case sugar was constantly absent (Chart VIII).

The case of K. P., to which reference has already been made, shows an interesting sugar curve which corresponds with the chloride curve. There is the initial fall followed by a rise to the normal zone associated with a remarkable improvement in the general features of the case, and the second fall occurring with a sudden and rapid deterioration.

III.—CALCIUM CONTENT.

Halverson and Bergeim[4] and several other investigators, have found that the calcium content of the cerebro-spinal fluid in the normal person is fairly constant, namely, about 5 mgrm. per cent., and that it is equivalent to about a half of the calcium content of the blood plasma. Repeated drainage of the subarachnoid space has been found not to change the calcium content. Leicher[5] in 29 cases found the average amount of calcium in the cerebro-spinal

fluid to be about 5 mgrm. per cent., and that this figure was unaffected by variations in the pressure of the cerebro-spinal fluid. More recent methods have shown a normal figure slightly higher, namely, 5·5 mgrm. per cent.

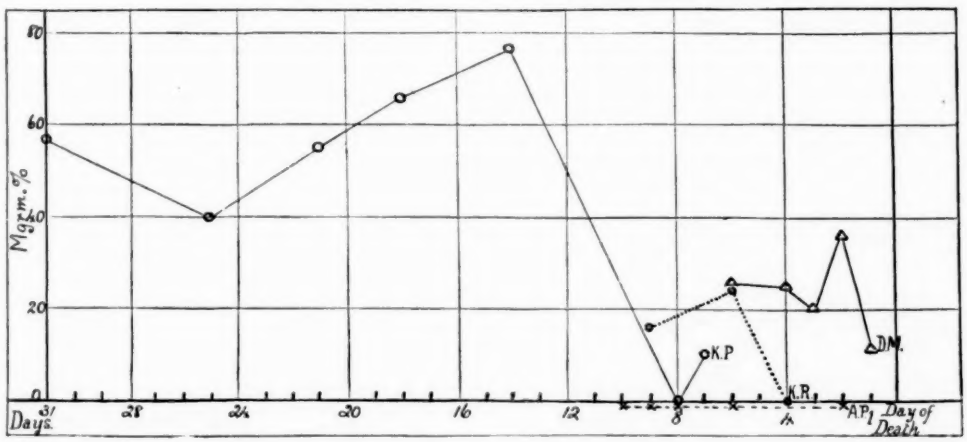
We have estimated the calcium content in children suffering from meningitis and in children with other diseases. In both groups we have included children who had convulsions and those whose illness was not characterised by this sign. No cases showing the phenomena of tetany are included.

According to our results which are given in Table 8 and in Chart IX, it is shown that, in patients having neither convulsions nor evidence of meningeal involvement, the calcium content of the cerebro-spinal fluid was found to vary from 5·1 to 6·5 mgrm. per cent. A comparable series of examinations in cases of meningitis without convulsions shows, on the whole, slightly higher figures. Further, in children suffering from meningitis with convulsions there is a still

CHART VIII.

Pneumococcal Meningitis in Children.

Sugar Curves plotted backwards from Death Point.



greater increase in the individual and average readings. This investigation was made primarily to determine whether there was any difference between the calcium content in convulsive as compared with non-convulsive conditions. By analogy with tetany and some other neurogenic disorders, it was thought that possibly a diminution in the calcium in the cerebro-spinal fluid circulating in the subarachnoid space might be a determining factor in the genesis of convulsions in meningitis. Our results, however, do not support the hypothesis; on the contrary, with the meningeal involvement there is almost always a rise in the calcium above the normal, and this is even more marked in the presence of convulsions.

The mean readings in the different groups are as follows:—

(*a*) Non-meningitic cases (no convulsions) 5·6 mgrm. per cent.
(*b*) ,, ,, ,, (with ,,) 5·7 ,, ,, ,,
(*c*) Meningitic cases (no ,,) 6·3 ,, ,, ,,
(*d*) ,, ,, (with ,,) 6·8 ,, ,, ,,

TABLE 8. CALCIUM CONTENT IN THE CEREBRO-SPINAL FLUID.

Case.	Age.	Diagnosis.	Calcium.
(*a*) Non-Meningitic cases without Convulsions—			mgrm. p.c.
L.A.	?	Polio-encephalitis	6·5
J.E.	5	Cerebral Tumour	5·2
C.H.	1¾	„ „	5·9
E.P.	3	Cerebellar „	5·4
V.C.	11	Encephalitis	5·6
V.C.	11	„	6·3
H.S.	9	Meningism	5·1
H.S.	9	„	5·2
E.H.	4	Polio-encephalitis	5·4
E.H.	4	„ „	5·7
W.H.	6	Encephalitis	5·1
L.M.	5	Meningism	5·2
D.C.	1	Encephalitis	6·4
D.C.	1	„	5·8
R.M.	?	Cerebral Tumour	5·2
D.C.	1	Encephalitis	5·9
		Average = 5·6.	
(*b*) Non-Meningitic cases with Convulsions :—			
M.G.	?	Epilepsy	5·8
B.	1	Measles	6·1
E.M.	4	Epilepsy	5·3
(*c*) Tuberculous Meningitis without Convulsions :—			
L.T.	8	Tuberculous Meningitis	6·1
C.S.	1½	„ „	6·8
K.W.	2	„ „	6·3
K.W.	2	„ „	6·5
K.W.	2	„ „	6·3
M.C.	2	„ „	5·7
M.C.	2	„ „	5·8
M.C.	2	„ „	6·0
M.C.	2	„ „	6·5
M.C.	2	„ „	6·6
M.C.	2	„ „	6·3
M.C.	2	„ „	6·1
A.C.	9	„ „	6·1
A.C.	9	„ „	5·7
A.C.	9	„ „	5·6
		Average = 6·3.	
(*d*) Tuberculous Meningitis with Convulsions :—			
F.J.	4/12	Tuberculous Meningitis	7·1
J.H.	3/12	„ „	5·9
A.S.	9/12	„ „	7·3
S.T.	1½	„ „	6·5
L.C.	6/12	„ „	6·8
L.C.	6/12	„ „	6·7
L.C.	6/12	„ „	6·4
L.C.	6/12	„ „	7·4
L.C.	6/12	„ „	8·0
I.B.	8/52	„ „	7·8
I.B.	8/52	„ „	7·3
I.B.	8/52	„ „	6·9
I.B.	8/52	„ „	6·7
K.C.	1	„ „	4·8
		Average = 6·8.	

(*e*) Meningococcal Meningitis (with Convulsions) :—

A.C.	4/12	Meningococcal Meningitis		..	..	..	..	7·4
A.C.	4/12	,,	,,	..	..	..	..	7·2
A.C.	4/12	,,	,,	..	..	..	..	9·5
A.C.	4/12	,,	,,	..	..	..	..	7·0
A.C.	4/12	,,	,,	..	..	..	..	7·4
A.C.	4/12	,,	,,	..	..	..	..	7·7
A.C.	4/12	,,	,,	..	..	..	..	7·3
A.C.	4/12	,,	,,	..	..	..	..	10·0
A.C.	4/12	,,	,,	..	..	..	..	7·7

Average = 7·9.

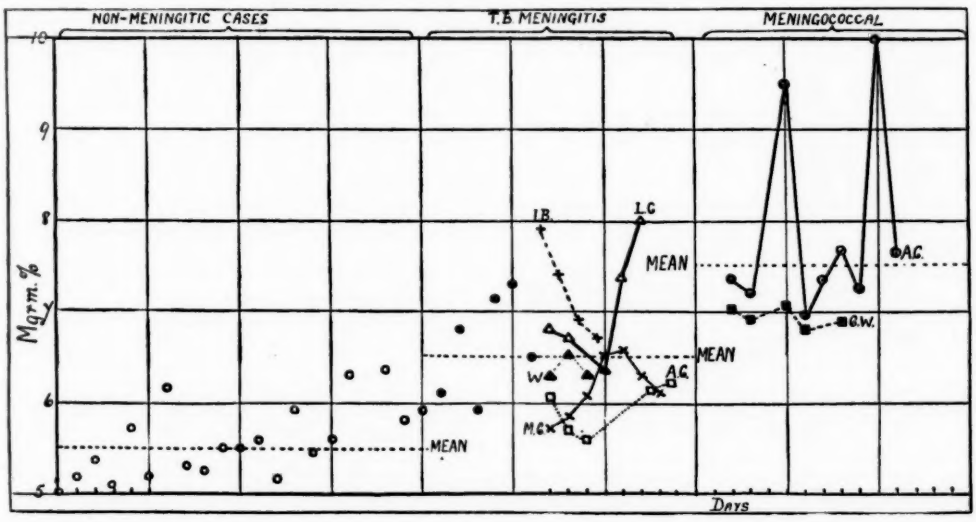
(*f*) Meningococcal Meningitis (without Convulsions) :—

C.W.	3/12	Meningococcal Meningitis		..	..	..	..	7·0
C.W.	3/12	,,	,,	..	..	..	..	6·9
C.W.	3/12	,,	,,	..	..	..	..	7·0
C.W.	3/12	,,	,,	..	..	..	..	6·8
C.W.	3/12	,,	,,	..	..	..	..	6·9

Average = 6·9.

CHART IX.

CALCIUM IN THE CEREBRO-SPINAL FLUID.



CONCLUSIONS.

1. The sugar, chloride and calcium contents of the cerebro-spinal fluid of children suffering from various diseases without meningeal involvement are within normal limits, with the exception that in acute pneumococcal infection a subnormal chloride content is present.

2. The current view that tuberculous meningitis is constantly associated with a low chloride content in the cerebro-spinal fluid is criticised. The necessity for considering the stage of the illness when reading bio-chemical results is indicated.

3. Comparisons are drawn between the chloride content in tuberculous meningitis and other forms of meningitis. When examinations are made at frequent intervals during the course of the illness, curves of the results show special features in each kind of disease. The tuberculous cases show a fall in the earlier stages and a rise in the later stages. Pneumococcal cases show a progressive fall towards the fatal issue. Meningococcal cases show the same in fatal cases but recovering cases show an elevation to within the normal.

4. The sugar curve in tuberculous meningitis is similar to the chloride curve in the same cases. A fall to zero point may occur during the illness and occasionally remain until death.

5. In fatal meningococcal meningitis and in pneumococcal meningitis a progressive diminution in the sugar content of the cerebro-spinal fluid occurs.

6. The sugar in the cerebro-spinal fluid in recoverable meningococcal cases shows an early fall followed by a gradual rise to normal. Therefore a sugar curve which commences to rise is of favourable prognostic import.

7. Evidence is given supporting the view that in non-meningitic and meningitic cases, the amount of chloride in the cerebro-spinal fluid varies to some degree with that in the blood.

8. A number of observations have been made on the calcium in the cerebro-spinal fluid. In non-meningitic disease it is shown that the calcium concentration is within the normal. Also that in conditions where inflammatory change occurs in the meninges the calcium is usually above the normal level, and this is more marked in the suppurative types of meningitis.

9. No calcium deficiency was detected in patients having convulsive seizures in meningitis.

We wish to express our thanks to Dr. Leonard G. Parsons, physician to the hospital and Dr. Evelyn Hickmans, bio-chemist, for their help and criticism; also to the Medical Research Council for defraying part of the expenses.

The bio-chemical methods used in this investigation were :—

(*a*) For cerebro-spinal fluid chloride : Whitehorn, *Journal of Biological Chemistry*, 1921, Vol. 46, page 450. Using 1 c.cm. of cerebro-spinal fluid.

(*b*) For cerebro-spinal fluid sugar : Maclean's Blood Sugar Method, using 0·4 c.cm. of cerebro-spinal fluid. *Bio-chemical Journal*, 1919, Vol. XIII, page 135. Each estimation was made within an hour of obtaining the specimen.

(*c*) For cerebro-spinal fluid calcium : Kramer and Tisdall (modified by Tisdall) using 4 c.cm. cerebro-spinal fluid. *Journal of Biological Chemistry*, 1923, Vol. 56, page 439.

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5. Leicher, *ibid.*

THE ÆTIOLOGY OF CŒLIAC DISEASE: PRELIMINARY COMMUNICATION ON THE BLOOD FAT.

BY

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For the purpose of this paper we will take as a definition of cœliac disease that put forward by R. Miller[1] in one of his recent communications on the subject: 'Cœliac disease is a digestive disorder arising in infants and young children who show no evidence of chronic intestinal or other organic abdominal disease: it is characterised by a persistent mal-absorption of dietetic fat which causes large stools containing an excess of split fat, enlargement of the abdomen, lack of growth and other symptoms.' As we hope to show later in this paper the term 'mal-absorption' is, we believe, incorrect, but for the moment the definition will serve. It excludes all forms of chronic enteritis and abdominal tuberculosis. For further details as to differential diagnosis on clinical evidence, Miller's paper should be consulted. The peculiar stools which are such a feature of cœliac disease are, however, also found in other diseases. In their recent paper on fæcal fat analysis in children Harrison and Sheldon[2] mention this point: 'the figures in tuberculous peritonitis show the same deviation from the normal as in cœliac disease.' Indeed the similarity between the stools of cœliac disease and those of abdominal tuberculosis in which there is obstruction of the lacteals has led Ryle[3] to put forward the suggestion that cœliac disease is due to lacteal obstruction. Two cases recently in the Hospital for Sick Children under the care of Dr. Thursfield illustrate this point.

Case 1. B. B., girl, aged $1\frac{10}{12}$ years. Admitted for loss of weight for three months following measles. The child had obviously wasted and the abdomen was enlarged with a large mass in the right lower part. The stools were pale, bulky and offensive. Analysis of the stool showed 67·8 per cent. of dried fæces was fat and of this 84 per cent. was split and 16 per cent. was unsplit. The blood fat was 0·145 per cent. (as fatty acid) 2 hours after a feed consisting of skimmed milk and Casec. The child went rapidly down and died.

At necropsy the abdomen was found to be filled with large masses of tuberculous glands, matting the intestines and obviously causing gross obstruction to the lacteals. No ulceration of intestine was found and there was no definite enteritis.

Case 2. F. A., boy aged $1\frac{3}{12}$ years. Admitted for wasting since the age of 11 months with bulky, offensive motions. The child was very wasted; abdomen distended, but without any signs of free fluid; no lumps could be felt. Analysis of the stools showed 38·97 per cent. of the dried fæces was fat, of which 74·05 per cent. was split fat. Blood fat 2 hours after a fat-free meal was 0·422 per cent. (as fatty acid). The child had curious attacks with sudden loss of consciousness. The temperature rose a few days after admission and he died.

At necropsy broncho-pneumonia was found. There were no changes whatever in the intestine, no enlargement of the mesenteric glands and microscopically the intestine and pancreas were normal.

These two cases, one of abdominal tuberculosis and the other regarded as cœliac disease, both showed many points of similarity in the wasting, the character of the stools and the passage of excess of fat in the fæces, mostly split in a normal manner. The striking difference lies in the blood fat estimated under almost identical conditions as to diet, time of taking blood, etc. It is so frequent in cœliac disease to talk of the mal-absorption of fat and to look upon the disease as essentially characterised by a failure of the intestine to absorb fat that it might be expected that the fat in the blood would be considerably reduced below normal. One year ago one of us (A. M.) had the fat in the blood of a cœliac child* estimated at the Middlesex Hospital and it was found to be higher than in a normal child of the same age. This surprising result, which was repeated on several occasions, led to the consideration that the fault in cœliac disease could scarcely be due to a faulty absorption. The work embodied in this paper was undertaken to investigate this subject still further.

Method of Blood-Fat Estimation.

The estimation of the blood fats in the small quantities of blood necessarily used in repeated observations in children is technically a difficult process and is liable to both individual and systematic errors. It is therefore desirable at present for each individual worker to establish his own normal values with the method he chooses to adopt.

With regard to the method to be used, the nature of the fat to be estimated must be considered. The ether-soluble fraction of the blood contains fats proper, lecithins and cholesterol and cholesterol esters. As the significance of these fractions differs it is necessary to make some attempt to distinguish them. It is now considered that cholesterol and its esters have but little to do with fat metabolism and that the lecithins and fats are probably of equal importance.

The more recent methods aim at estimating only the saponifiable matter, that is, the fats proper and the fatty acid fraction of the lecithins. The estimation of the ether soluble phosphorus will give an indication of the proportion of the fatty acids to allot to the lecithins. The method at present used differs somewhat from other methods in that only fatty acids yielding insoluble calcium soaps are estimated. The values obtained do not differ greatly from those given by other workers.

As with blood sugar, so with blood fat, the time and nature of the preceeding meal must be considered. The amount of information at present available with regard to the effect of fat meals on the blood fat is not by any means as complete as could be desired. That there is a rise, with a maximum between two and five hours after a fat meal is generally agreed. The degree of this rise varies considerably according to various factors, e.g., a smaller rise occurs when animal fat is given than when vegetable fat is given. In dogs frequent repetition of the fat meal (which presumably was greater than that normally taken) resulted in a progressively smaller increase in the blood fat.

* Dr. C. E. Lakin has kindly allowed us to mention this patient who was under his care.

Again, the nature of the food taken with the meal causes a difference, there being a larger rise with meat and fat than with bread and fat (Bang[4]). These results have mainly been obtained in dogs and adult men. Pending the investigation of these various points in children, it has been considered sufficiently accurate for purposes of comparison to take the blood at the same time of day in each child without disturbing their usual diet.

Etiology of Cœliac Disease.

The problem of the cause of cœliac disease has attracted the attention of many workers. Herter[5] in his original publication on intestinal infantilism in 1908, believed that the disorder began as a chronic inflammatory process in the intestines, and he was inclined to favour a bacterial cause. This view is still prevalent in American literature, and Sauer[6] in a recent paper has called attention to certain evidence which he believes shows that cœliac disease may be transmitted from one child to another. It is probable that confusion has arisen with regard to a possible bacterial origin because "chronic intestinal indigestion" and "chronic enteritis" have not been sufficiently separated from cœliac disease by many writers. Miller and others have particularly gone into this point, and Miller's paper already mentioned should be consulted as to details. The pancreas has been blamed, but tests for pancreatic efficiency are normal in cœliac disease. In any case the fat in the fæces is normally split and Bauer[7] has investigated the intestinal ferments by means of a duodenal tube in a case of cœliac disease and has shown that they are present in the same amounts in the presumably normal child with similar variations as regards feeding and fasting. Their digestive powers are also similar. (The actual substances investigated were bile, lipase, trypsin and amylase). The view that the lacteals are obstructed has already been mentioned and may be dismissed by saying that there is not sufficient evidence in its favour and the facts that cœliac cases do not develop tuberculosis, nor can mesenteric glands be felt, seems to dispose of it as the cause of cœliac disease. Miller's own view on deficiency of the bile-salts is admittedly arrived at by a process of exclusion and has not much evidence in its favour, and at the moment it may be said that the ætiology of cœliac disease is unknown. This is, we believe, largely because of a fundamental misconception of the meaning of excess of fat in the stools.

The common view is that absorption is at fault and that by cutting down fat in the diet this can be prevented to a large extent by presenting the intestines with a limited amount of fat to deal with. Bauer[7] has indicated that absorption of fat seems to be as readily attained experimentally in the child with cœliac disease as in the normal child, and the work of Hill and Bloor[8] and of Speery and Bloor[9] seems to indicate that the fat in the fæces appears to have no direct relationship to the fat in the food in many cases 'but represents rather some form of excretion from the intestinal tract' (Hill and Bloor, 1922). In the early experiments these workers reached the conclusion that fatty substances were to be found in the fæces whether present in the food or not and that fat in the food increases the fæcal fat, but only to a comparatively small extent.

Of the experiments Hill and Bloor said " taken altogether they indicate a continuous output of ' fat ' in the fæces of a constant composition independent of the diet.' In a later paper Speery and Bloor[9] described further experiments on the ' fæcal lipoids ' and they concluded that ' the most probable source of the fæcal fat seems to be excretion from the blood, either directly or indirectly, as is evidenced by similarity of the fæcal lipoids to those of the plasma.' They believed that there were two possible ways in which fat could be excreted from the blood : either as a true excretion of unusable material, waste fat from lipoid metabolism, or as a leakage of usable fat due to a fat plethora and analagous to alimentary glycosuria on a high sugar intake.

The conclusions only are quoted here, but the original papers contain records of many experiments in support of the views put forward, and if the work is accepted as correct, then a possible explanation for cœliac disease lies in the high blood fat associated with excretion in the fæces of fat which has " leaked " from the blood. In other words the primary fault in cœliac disease is not a mal-absorption of fat, but a mal-utilisation of fat, a defect of fat metabolism possibly analagous to the defective utilisation of sugar in diabetes. It is suggestive in this connection that in many cases of cœliac disease carbohydrates are not normally dealt with, and indeed the association of cœliac disease and diabetes mellitus has been described in a child of seven years old by Poynton and Cole[10]. It is also interesting to note that a high blood fat is found in many cases of diabetes where it is fairly definite that there is a failure of fat metabolism as well as carbohydrate metabolism.

Conclusion.

We have not investigated sufficient cases to establish the theory here put forward, but as a working hypothesis for further investigation we would suggest that cœliac disease is a primary disorder of fat metabolism associated with an increase in the fat in the blood and in the fæces, where possibly it is being excreted.

We are indebted to the Physicians of the Hospital for Sick Children, Great Ormond Street, for permission to make use of their cases.

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TABLE 1.

BLOOD-FAT ESTIMATIONS IN NORMAL CONTROLS.

Case.	Age in years.	Disease.	Fatty acid in blood. %
E. K.	$1\frac{2}{12}$	Otitis Media	·163
B. W.	4	Rheumatic Carditis	·142
E. P.	$2\frac{3}{4}$	Cerebral Tumour	·208
P. D.	$2\frac{2}{12}$	Unresolved Pneumonia ..	·173
M. R.	$2\frac{10}{12}$	Diarrhœa (stools normal) ..	·142

Blood taken in each case about 11 a.m., that is, $2\frac{1}{2}$ hours after a light meal.

TABLE 2.

BLOOD-FAT ESTIMATIONS IN PROBABLE CASES OF CŒLIAC DISEASE.

Case.	Age in years.	Comments.	Fatty acid in blood, %
D. B.	3	Improving	·275
E. B.	$2\frac{7}{12}$	Improving	·280
D. S.	$3\frac{9}{12}$	Not doing well	·530
J. A.	$3\frac{9}{12}$	Improving	·280
B. R.	$2\frac{1}{2}$	(See note below)	1·17
,,	,,	,, ,, ,, ...	1·15
,,	,,	,, ,, ,, ...	·51
J. S.	$4\frac{1}{2}$	,, ,, ,, ...	·62

The blood in each case taken about 11 a.m. after a small meal at 8.30 a.m. containing no fat. The last two cases were private patients. Blood was taken three hours after a meal very low in fat. These two cases were investigated before treatment was begun.

FUNCTIONAL VOMITING IN NEWBORN AND PREMATURE INFANTS.

BY

WILLIAM EMDIN, B.A., M.D.

In making a study of the symptom of vomiting in the newborn and premature infant, the descriptions here mentioned and the conclusions drawn are based on observations made in the wards of the Universitäts Kinderklinik and the Maternity Wards of the Peham Frauenklinik at Vienna. Pirquet has instituted a method of recording by means of symbols the exact description of the act of vomiting so that the case sheets give details of the progress of the case in this direction, thus facilitating the study of the cases.

I. Anatomy and Physiology in connection with the Act of Vomiting.

The investigation of the infantile stomach by means of X-rays has opened up a hitherto undefined field, viz., that of the anatomy and physiology of the stomach during life. The form and position of the stomach is very similar to that of the adult, except that, as recent investigations seem to show, the position is usually horizontal rather than vertical. We can distinguish five parts ; the fundus, body, pars angularis, canalis pylori (or pyloric antrum) and the pyloric valve.

The œsophagus runs downwards, forwards and to the left to meet the stomach. Thus gruels and the more solid foods are given a propulsion towards the fundus, whereas fluids pass along the so-called gastric canal of Lewis[10] (' Waldeyerische Magenstrasse '), an anatomical landmark which was demonstrated by Lewis on the stomach wall of the human embryo, running along the lesser curvature from the antrum cardiacum to the incisura angularis. The lesser curvature is directed dorsally in the infant. Milk passes from the cardia to the pylorus and thence to the duodenum without entering the fundus ventriculi. The upper part of the œsophagus contains voluntary muscle which passes also, to some extent, into the lower portion. There is no evidence of the presence of striated muscle at the cardiac sphincter : that is to say, there is no voluntary control at this area.

The radiographic appearance of the stomach varies with the type of food ingested. When the content is fluid, an oval, pear-shaped or even " bagpipe " contour may be noted. This depends to some extent also on the amount of air swallowed, which is often in considerable quantity when the diet is a fluid one. When gruels have been taken, the infantile gastric organ is contracted, circular or oval in shape, and barely reaches the mid-line. It contains

perhaps a small air bubble, or as is frequently the case, no air at all (Rogatz[14]). Various observers have shown that the ' peristolic function ' which the stomach has of contracting down upon food occurs in infants as well as in adults, especially when the more solid foods, *i.e.*, gruels, have been ingested. Solid food, therefore, has two distinct advantages when used as a therapeutic measure in the inhibition of vomiting ; first, the food is surrounded by the contracting stomach wall, thus hindering loss by emesis ; and secondly, little air is swallowed in the process of ingestion.

The pyloric antrum (" Magenmotor " or canalis pylori of Müller) is of interest because it is in this area that the pressing out movements of the stomach originate, as do also the spastic and anatomical alterations which accompany pyloric stenosis (Wernstedt[19]). This has been termed the " contraction phenomenon area " because it is here that hour-glass contractions are seen by means of X-rays in the perfectly normal infant.

Swallowed food, chiefly milk in infancy, having entered the stomach, peristaltic waves which originate superficially about the middle of the stomach (Cannon[2]) and from the greater curvature (Theile[18]) pass towards the pylorus, penetrating deeper and deeper, and resulting in the complete closure of the lumen of the pyloric antrum which subsequently commences to contract. The pyloric valve then opens. Marked motor activity on the part of the stomach has evidently some effect on the opening of this sphincter and thus hyperacidity cannot be the only factor concerned in this process. The ingested milk is thus thoroughly mixed with, and rapidly acted upon by, the gastric juices. Curd formation owing to the action of rennin takes place, thus affording proof that the milk has actually reached the stomach.

X-ray investigation shows that a bismuth meal begins to leave the stomach within five minutes of entrance, the total emptying time being from $1\frac{1}{2}$ to 3 hours (Pisek and Lewald[12]). Milk dilution increases the rapidity of evacuation to a certain degree only ; solid food on the other hand is passed into the duodenum with a rapidity varying inversely with the degree of concentration. An increase in the fat content lengthens the emptying time. As a result of recent investigation, Rosenbaum[15] believes that protein is an important factor in inhibiting pyloric opening, and he maintains that the relatively higher protein content of cow's milk as compared with that of human milk is the chief cause of the slower digestion of the former.

With regard to hunger movements, Carlson[3] states from observations on the stomach of newborn and premature infants that such movements are present as in the adult, but are of greater frequency and relatively greater vigour. They commence at the cardia. His work has been confirmed by Taylor.[17]

II. Vomiting in the Newborn Infant.

Before entering on a consideration of vomiting in the newborn infant it is necessary to mention that vomiting not associated with nutritional,

bodily or neurotic disturbance may occur one or more times during the first day or so of life. This consists in the return of foreign substances swallowed during the birth period. The vomitus, which is usually a colourless, slimy fluid containing perhaps brown, hæmorrhagic masses incorporated in it, may be copious in amount and consist of liquor amnii, vaginal secretion, swallowed blood, etc. (Reuss[13]).

With the commencement of food assimilation, vomiting is an extremely common occurrence. Various factors are concerned in its causation. A breast which too readily yields its secretion may lead to over-feeding and the excess of milk is returned, usually immediately. Swallowed air when eructated may bring with it some of the milk, or, interference with the breathing may be the cause, as occurs when the mother presses the child too forcibly against the breast, thus occluding the nostrils and necessitating the interruption of feeding in order that the infant may breathe. Congenitally narrow nostrils or nasal catarrh may have the same effect, and this break in the feeding is very often accompanied by the regurgitation of milk from the baby's mouth. A fair quantity of the food may be lost in this way.

Apart from this, however, vomiting which cannot be attributed to the above causes on the one hand or infections on the other, occurs with a frequency which is striking. On observing the newborn infant at the breast, it may be noticed that at times there is a cessation of suction and milk is seen to well up in the mouth of the infant and overflow the lip margins. There is no force behind this flowing milk, nor are curds present. This manifestation is not correctly included under the term infantile vomiting, because the milk has never reached the stomach. The most probable explanation (Pirquet) is that in the newly born infant there is a lack of co-ordination between the muscles concerned in the act of swallowing, and the child has not yet learned to swallow properly. This art is, however, rapidly acquired. To this type I would apply the term "pseudo-vomiting" in contradistinction to true vomiting of the milk which has actually reached the stomach.

Apart from this pseudo-vomiting there is no doubt that actual vomiting occurs with relative frequency during the early period of infancy. Schick[16], while studying the effect of various forms of nutrition on the newborn infant was struck by the frequency with which vomiting became manifest. Even when a concentrated food was given ("Dubo" or doubly concentrated food) he noticed that vomiting occurred in cases where overfeeding was out of the question, as the food intake had been carefully determined. Nor could the type of food given have been the causative agent because when the mother's milk was given in small quantities, or even when the milk was replaced by small amounts of saccharine-sweetened tea, vomiting still occurred. We have then, at this period, not only pseudo-vomiting, but also true vomiting, the infant being unaffected at the time or later, *i.e.*, no harmful effects follow.

I commenced the study of vomiting in the newborn infant by investigating three hundred consecutive cases during the first week of life. Of these, if we consider both the true and pseudo-vomiters, about 55 per cent. of the total

number returned the milk. In order to study true vomiters during the first days of life pseudo-vomiters were disregarded and only those infants considered whose vomit contained curdled milk, or was of such amount and frequency as to make it clear that the milk had actually been in the stomach. It should be remembered that it is possible for the milk to have been swallowed and then vomited before the rennin has been able to produce a curd.

The following were the results obtained :—

1. Excluding pseudo-vomiters, of which there was a good number, 64 of the 300 were true vomiters, a percentage of 21·3.

2. Of these 64 cases, 36 were male and 28 female infants. The total number of male and female children being 161 and 139 respectively, gives a percentage of 22·4 male and 20·2 female vomiters, which shows no special sex tendency towards vomiting.

3. With regard to the relation of body weight to vomiting, of the above mentioned 64 vomiters, 14 were born with a body weight below that of 2,500 grammes (5 lb. 8 oz.) and of the total 300 cases, 39 were below this weight at birth so that the percentage of vomiters below 2,500 grammes birth weight rises to 36. When we compare this figure with the percentage figure of infant vomiters above 2,500 grammes weight at birth (50 out of 261 or 19·2%) a more pronounced tendency towards vomiting is demonstrated on the part of the premature and weak infants even during the first week of life.

4. Vomiting usually commences about the end of the first day or on the second day of life, *i.e.*, when milk is first assimilated. This type of vomiting is purely physiological in character in that it produces no ill effects on the infant. There is probably some relation between this and the drop in the weight curve which takes place during the first days of life, but the vomiting is not the essential cause of this drop, because a similar temporary loss in weight occurs in infants who vomit little or even not at all.

5. The vomiting increases in frequency during the second and third days, and perhaps the fourth day of life, after which, in most cases, it rapidly decreases in frequency and amount, so that by the sixth or seventh day very few infants vomit much. The vomit is composed of milk in which curds may be seen, and it may be ejected from the mouth with a slight amount of force and is often found lying on the bedclothes a little distance from the infant. Usually, however, there is little force behind the act. Pseudo-vomiting, on the other hand, is more common during the first two or three days, is always flowing in character and disappears towards the end of the week as the infant acquires control over the muscles concerned in the act of swallowing.

6. Vomiting may occur in infants of excellent bodily development without being followed by harmful effects. In nine of the cases under consideration the minimum weight was 3,300 grm. (about 7½ lb.) and the maximum 4,000 grm. (8½ lb.) and yet in these cases vomiting occurred frequently and at times fairly copiously. It is interesting to note that in two of them bile appeared in the vomit without being of any special significance, although this occurred

during the first days of life. There was no subsequent evidence to prove that the infants were at all affected by the appearance of this abnormal substance in the vomitus ; in fact, there was not even an accompanying loss in weight, the infants developing normally and rapidly.

The subsequent history of these cases was difficult to determine for the reason that being normal children they soon left the clinic and the observations of the mother with regard to vomiting are insufficiently reliable. A study of case records goes to show that most normal infants cease vomiting, except for periodic bouts of short duration, by the end of the first week. Vomiting may continue in perfectly normal infants for two, three, or even more weeks without being pathological ; in fact, if unaccompanied by harmful signs, such as loss in weight, this manifestation may be totally disregarded. Such cases are, however, comparatively uncommon, and as a general rule obstinate vomiting continuing for a longer period than the first week should be looked upon with suspicion and the possibility of habit developing should be kept in mind : that is, if all other possible causes, such as organic disease, can be excluded.

III. Vomiting in the Premature Infant.

Under " Prematures and Weaklings " are included those infants with a birth weight of less than 2,500 grm. (5½ lb.). A few facts in connection with vomiting in the immature infant are of importance. The stomach of the premature infant is extremely small, its capacity in an infant weighing at birth 1,000 grm. (about 2 lb.), being not more than five cubic centimetres and often as little as two. Further, the closure mechanism of the cardiac sphincter is poorly developed, in fact a sound can be readily passed without much resistance being encountered. Thus food is easily able to leave the cardiac end of the stomach. The infantile mortality of the premature and weakling is extremely high, being due among other factors to the frequency of the complication, pneumonia, the irregularity of thermo-regulation, etc., the mortality increasing by leaps and bounds in inverse ratio to the body weight. Thus the mortality of prematures under 1,000 grm. weight at birth is, during the first year of life, as high as 94·4 per cent. whereas the average mortality for all prematures during the first year is about 50 per cent. (Ylppö[21]).

In all, a study was made of some sixty cases of premature and weakly infants. At the Universitäts Kinderklinik at Vienna, the dietetic method of treating premature infants is to give a concentrated food of small bulk. Milk to which 12½ per cent. sugar is added (so-called " Sesquibo ") is commonly used. Cow's milk, or better, human milk is given to the infant. Where necessary doubly concentrated human or cow's milk may be used. This double concentration is obtained by the addition of 17 per cent. sugar, thus giving a double caloric value to the mixture. For example, cow's milk has a caloric value of 67 to the 100 grm. (3½ oz.). If we add to this, 17 grm. of sugar (67 calories) we have a mixture when boiled weighing roughly 100 grm. and containing 134 calories, a double concentration (the so-called " Dubo "). In very small and

delicate infants a commencement is made with small and frequent feeds of unaltered mother's milk. Naturally, no hard and fast rule can be laid down to cover every contingency, and the above is but a résumé of the general principles which are applied.

On studying premature and weakly infants, I found it was possible to divide them, as in those of normal weight, into distinct groups, the vomiters and the non- (or slight) vomiters. The vomiters were further subdivided into those which died and the survivors.

To commence then with those infants which survived. Of a consecutive series of thirty-two cases which came under my consideration, only twelve survived. Most of the survivors vomited frequently during the first two weeks of life, ceasing, with two exceptions which continued vomiting up to and including the second month, by the third week. The study of other cases of prematurity has shown that many infants, perfectly healthy, with good stools and no sign of infection, gaining weight steadily, have vomited consistently for a long period, even up to and including the third or fourth month. The following is a typical example of such a premature vomiter :—

Case 1. G.T. Weight at birth 1,600 grm. Fed on Sesquibo and showed a steady gain in weight from the commencement. No nutritional or general disturbance of any kind, and yet the infant vomited continually 3 to 5 times daily, often with some force. The infant was still vomiting at the end of the first month.

All premature infants do not necessarily vomit. Of the twelve cases mentioned, only three vomited for a period longer than two weeks, two continuing into the second month. The percentage of vomiters is far higher than among children weighing 3,000 or more grm. at birth ; thus the premature infant seems to have a greater tendency towards vomiting than his more fortunate brother.

To state that weight is the only important factor is an exaggeration. The birth weights of the twelve survivors were : 1,740, 1,700, 2,010, 1,720, 1,800, 1,200, 1,500, 1,800, 2,200, 1,800, 1,760 and 2,100 grm. respectively, nine of the twelve weighing less than 2,000 grm. ($4\frac{1}{4}$ lb.). We know that the smaller the birth weight the greater the tendency towards vomiting, infection and death. The above cases show, however, that weight is not the only deciding factor with regard to survival. In my opinion, at least two important accessories which in the premature infant are often lacking, are, a sufficient constitutional development to enable the weakling, however small, to withstand the attacks of infection, and, what is essentially influenced by the above, a sufficient inhibitory control of vomiting. I am assuming, of course, that the infant has received reasonable and intelligent care and has not been unduly exposed to infection, as is often the case owing to ignorance. The question of inhibitory control which in the premature infant is often defective, will be discussed more fully when the possible ætiology of vomiting in the newborn is considered. It might be argued that the premature infant is prone to infection (hence the high mortality), which of itself is the cause of vomiting. Although this may be true to some extent, another possibility might be con-

sidered, viz., that the premature infant, owing to its tendency to vomit, loses food and thus is further weakened. This still further lowers its congenitally insufficient resistance and vitality, a vicious cycle being established.

The survivors may, then, be vomiters or non-vomiters. In connection with the non-vomiters it must not be forgotten that this type of infant at this clinic is fed on a concentrated diet which in itself ought to act to some extent as a deterrent from emesis. With regard to the second group of survivors, viz., those which vomit for a long period in spite of the fact that they are receiving a concentrated diet, and which thrive in spite of this if properly looked after and given sufficient to cover the food loss, it is possible that even in a well developed constitution the inhibitory control, at first insufficient, subsequently leads to the development of a habit. In other words, this infant may be likened to the habitual or neurotic type of vomiter with a higher birth weight.

The act of vomiting in premature infants is rarely forcible. As a rule it starts to vomit more slowly than the normally developed child, but soon begins, if a vomiter, to vomit more frequently, obstinately and copiously, especially when a complication, whether gastro-intestinal or otherwise, is present. We often find included in the vomitus of the premature infant adventitious substances such as mucus, blood, and bile. During the first few days of life the gastric mucous membrane of the weakling is frequently covered by an abundant layer of mucous secretion, and many of the infants have a mucous membrane impregnated with blood. It is often possible to discover post mortem minute multiple ulcers in the mucous membrane, and these ulcers are held to be an important source of entry of sepsis and infection-causing bacteria.

The non-surviving premature infants, most of whom vomit, commence vomiting infrequently, but gradually begin to vomit more often. The following is a description of a typical example. The infant died on the ninth day of life and showed so many features in connection with the vomiting of the moribund weakling that it will be considered in detail.

Case 2. F.R. Born on November 2nd, 1926, weighing 1,150 grm. (about 2 lb. 6 oz.). Icterus was a prominent feature and deepened as time progressed. The infant was placed in an incubator and fed on human milk, at first receiving 64 c.cm. per day and later 120 c.cm. Owing to feeble sucking it was necessary to feed the child by means of a tube. The vomiting was actual vomiting, but small in amount at first. As early as the second day the presence of bile in the vomit was noted. On the fifth day, the infant vomited several times, bile appeared on two occasions, and the character of the vomiting act altered. Where before it had been of a flowing nature, it now became forcible and more frequent owing probably to the grip of a pneumonic infection. Then the forcible vomiting gave place to a more placid type, due possibly to exhaustion and the defeat of the bodily resistance. With the progress of the case bile again appeared in the vomit, which contained also mucus, but the act was no longer forcible, but flowing in character. Finally the child died, death being preceded by vomiting of a flowing nature, the vomitus containing traces of blood as brownish-red streaks.

One point of especial interest was observed in connection with this infant, namely that the child vomited through the nose. This occurred twice and on both occasions bile was contained in the vomit, small in quantity the first time when the vomit was slightly projectile in character,

but more copious on the second occasion, which took place shortly before death. The latter type is the more common and I have known it to occur with relative frequency in moribund premature infants. One usually notices that the bile-stained fluid flows out of the nostrils and also the mouth just before death, and this manifestation is, in my opinion, of extremely grave prognostic significance.

The post-mortem examination showed a lobular pneumonia, physical signs of which were present before death. The temperature curve was interesting in that there was no pyrexia present in spite of the critical condition of the child. This is a common finding where premature infants are concerned. On the eighth day a drop in temperature to 33 degrees Centigrade (91 degrees F.) was noted, and on the day of death, the temperature rose to just above normal. Just before death, also, a small amount of blood appeared in the vomit, a manifestation which I have noted in some six other moribund premature infants.

The case presents so typical a picture that it is unnecessary to go further into detail except to note the increasing frequency of the vomiting, the alteration in character, the presence of abnormal accessory substances in the vomited matter, and the flow of the bile-stained vomit through the nose. Finally, the type of vomiting in association with the presence of bile is worthy of note. (1) On the second day of life, a small amount of bile-stained fluid was vomited, unmixed with milk; (2) on the fifth day, the act was forcible in character and the vomit contained mucus, bile and also milk; (3) on the day of death, there was non-forcible flowing vomiting, the vomitus being more copious than previously and containing mucus, bile and milk.

The above illustrates many of the typical findings in moribund premature infants. Several other cases showed similar findings, but it is unnecessary to quote them as they would be more or less a recapitulation of the above.

IV. The Significance of Bile and Blood in the Vomit.

We have seen that the appearance of bile in the vomit during the first few days of life is important, especially where the premature infant is concerned, but not necessarily of grave prognostic significance. Referring to the nine normal infants considered in the second section, it was noted that bile appeared in the vomit of two, unaccompanied by any harmful symptoms whatsoever. Further, it was found that in both these cases the amount vomited was small and the vomited matter contained no milk, being composed purely of a mixture of bile and gastric secretion. It is worthy of note, also, that Case 2, where the vomit contained bile on three occasions, showed this same feature on the first occasion when probably still in the non-infected stage, viz., the bile was unmixed with milk. This might lead to the conclusion that the momentary relaxation of the pyloric sphincter and the regurgitation of some bile into the empty stomach is less pathological than when the stomach contains food, because in the latter case the bile must be forced against the pressure of the stomach contents.

Many authors attach the gravest significance to the presence of bile in the vomit, especially in earliest infancy. Langstein[8] advises that these newborn infants be treated as though having severe nutritional disturbance. With regard to premature infants there is no doubt as to the importance of this sign, especially when copious vomiting occurs. In hitherto normal infants, if the vomiting is not too copious and of infrequent occurrence, especially if there is no coincident loss of weight, little significance may be attached to it. These conclusions were arrived at after a study of a number of cases and case records,

Copious biliary vomiting, then, is a valuable guide to prognosis in early infancy, and its causation of great importance. A common cause of this type of bilious vomiting is found in congenital defects of the intestinal tract. The following was such a case and from the differential diagnostic point of view was interesting :—

CASE 3. M.H. Mongol. Premature infant with congenital heart lesion. Vomited from birth and only lived two days. Analysis of the vomiting was as follows :—

1st day. Infant vomited eleven times. Bile was copious in amount and for the most part the vomiting act was projectile in character.

2nd day. Child vomited nine times and then died. On this day, the vomit was non-projectile. Post-mortem examination showed an atresia of the duodeno-jejunal junction.

Bilious vomiting is also found where a temporary atresia has occurred, as for example in intussusception.

The following case demonstrates the fact that biliary vomiting may occur copiously and frequently where there is no organic lesion and thus probably has some nervous influence as the cause.

CASE 4. M.V. A premature infant with a birth weight of 3¼ lb. Vomited copious bile-containing fluid from the first day of life. Infant had difficulty in breathing from birth and ultimately on the fourth day respiratory cessation occurred and the child died. Post-mortem examination showed a ruptured tentorium cerebelli with severe epi- and sub-tentorial hæmorrhage.

1st day. Child vomited seven times and on four occasions bile was present in fairly large amounts.

2nd day. Child vomited fourteen times and on six of these occasions the vomited matter contained bile, and was forcibly ejected.

3rd day. Child vomited twelve times, mostly projectile, and bile was found in the vomit each time.

4th day. The child died, after vomiting eight times, bile being present in nearly every specimen of the vomitus.

In this case the causative agent was irritative impulses from the central nervous system and the marked effect of cerebral control in so under-developed an infant is interesting. Here the vomiting act was decisive in character and forcible from the start with the early and persistent appearance of bile in the vomit.

A comparison of this case with Case 3 in which there was an organic gastro-intestinal malformation shows the power of cerebral control, even in an under-developed and immature infant.

Considering now vomiting in relation to icterus, icterus occurs in infancy in the following conditions : (1) Icterus neonatorum ; (2) Icterus neonatorum gravis ; (3) Symptomatic icterus, as in acute infections, sepsis neonatorum, etc. ; (4) Congenital syphilis ; (5) Congenital atresia and narrowing of the large bile ducts.

Icterus is also an accompanying manifestation in premature infants. Most of the above mentioned do not come under the heading of functional conditions. I have seen one case of congenital atresia of the common bile duct, but as would be expected, no bile appeared in the vomit. Unfortunately no case of Icterus neonaturum gravis presented itself, and with regard to congenital syphilis, I would only remark that in several cases vomiting of bile-containing material occurred. In a series of cases of Icterus neonatorum, I

found nothing of special importance with regard to vomiting, as might be expected in a physiological condition of such benignity. Once or twice bile appeared in the vomit, but it is not a constant feature and is probably similar in origin to the bile present in the vomit of the healthy infant.

How may we recognize the presence of bile in the vomit ? This is not always easy. The colour varies, with the concentration of the bile and the medium in which it lies, from a light yellow to a dark green. Further, it may be diffused throughout the vomited substance or present as light yellow dots of varying size. If the vomit is diffusely bile-stained and contains cow's milk, the bile may tinge the milk a light yellow colour so that the appearance is that of colostrum milk, and as the majority of the newborn infants arebreast fed and thus receive at first the colostrum-rich breast-milk which has a yellowish tinge, the latter, if vomited, must not be confused with bile-containing vomit. On the other hand, the milk may be spotted with chrome yellow dots, or, if in greater concentration, greenish masses, which might easily be confused with the greenish mucus produced by nasal catarrh which has been swallowed and vomited. The distinction is not always easy and chemical examination may be necessary in order to be certain. Where the bile is mixed with gastric juice alone, *i.e.*, in the absence of milk, the colour is usually of a darker green and diffused throughout the fluid.

Blood also, when present, may be diffused throughout the vomited fluid, which is then of a light red colour. This is uncommon during infancy except where melæna neonatorum is present. It may appear as dark brownish shreds (" coffee-ground " vomiting) or even as small brownish masses. Hæmatin, which is the substance present in these latter types, is formed by the action of the hydrochloric acid of the gastric juice on the hæmoglobin.

Newborn and premature infants show a definite tendency toward hæmatemesis as well as to other forms of bleeding. At no other period of life is hæmorrhage into the skin, internal organs and mucous membranes so prevalent (Langstein and Lotte Lande[9]). This does not fall under the heading of the hæmorrhagic diathesis (Ylppö[10]), but the following factors have probably some relation to bleeding during the early days of life :—

(*a*) Birth is accompanied by the congestion of the blood vessels and this is especially marked when there is an associated asphyxia. The higher viscosity and specific gravity of the blood at this period are probably aggravating factors.

(*b*) The blood vessels are easily damaged.

(*c*) Icterus, a common manifestation in newborn, and always present in premature infants, has a coagulation-inhibiting tendency.

Premature infants show a tendency towards hæmatemesis, as in Case 2, mentioned previously, where blood was vomited just before death. In six other moribund premature infants I found blood in the vomit.

The following three cases were infants suffering from melæna neonatorum. It is worthy of note that all three were premature infants.

CASE 5. H.K. Born on August 4th, 1926. Weight 4¼ lb. On the first day of life the child had many bloody stools, but no blood in the vomit. Gelatin was injected intramuscularly as a therapeutic measure, and blood ceased appearing in the stools after the third day. No blood appeared in the vomit; but the child showed itself to be a bad sucker and actual vomiter from birth. The vomiting became habitual (3 to 5 times daily) although not projectile. Appetite and stools good. Bile appeared in the vomit twice with apparently no ill effects. At the end of the second month the child was still vomiting, although little, and this ceased entirely soon after.

CASE 6. F.B. Two days old. Weight at birth under 5 lb. Vomited blood (red) on the third day of life and then once daily until the infant was seven days old. The infant soon showed itself to be a persistent vomiter, vomiting 4 to 6 times daily, chiefly non-spastic in nature. A doubly concentrated diet of cow's milk and, when obtainable, mother's milk, was given, and the infant began to vomit less frequently. After six weeks of treatment the habit was broken. During the first two weeks the vomiting was forcible in nature, but later became more atonic. The vomited matter contained curdled milk and sometimes mucus.

CASE 7. J.S. Birth weight 4 lb. 6 oz. When 18 hours old the infant vomited bloody fluid which was of a light red colour and contained coffee-coloured masses. Nothing pathological in the mouth or throat was visible. With treatment the child vomited blood only once more. In this case, there was the development of habitual vomiting, often of a spastic nature, six or seven times daily. After the fourth week, with the use of a concentrated diet, the vomiting became less forcible in character, and in the sixth and seventh weeks there was a marked change for the better.

The above cases illustrate the point that there seems to be a tendency towards vomiting where melæna is present. Whether the presence of melæna has some effect in furthering the vomiting habit is open to conjecture, but as this condition commonly occurs in premature infants, who also show a greater tendency to vomit than infants with a higher birth weight, the immaturity may have some effect in this direction, aggravated perhaps by the melæna.

The origin of true melæna is still unknown. Associated with this condition we often find multiple small ulcers of the stomach and duodenum, and perhaps ulceration of other parts of the alimentary tract. These may, however, be entirely absent, and at the post-mortem examination a diffuse hæmorrhage, or a hyperæmia of the mucous membranes, may often be found. The presence of the ulcers might be explained in a number of ways. The action of the gastric juices on the physiologically hyperæmic areas, or punctate bleedings of the mucous membranes producing erosions and peptic ulcers which in turn erode into larger vessels and thus give rise to further hæmorrhage. Again, hæmorrhage and tissue digestion following thrombosis of the small intestinal vessels, resulting from vasomotor ischæmia, might give rise to such ulcers. There is a theory also that conditions of severe central nervous irritation may cause hæmorrhages of the intestinal mucosa, the action of the gastric juice producing ulceration. Finally, we know that the vessels of the newborn infant are fragile and may thus be readily induced to bleed by toxins either bacterial or non-bacterial (toxins of pregnancy or those produced by a damaged or an inefficiently acting liver).

V.—ÆTIOLOGY OF VOMITING IN NEWBORN AND PREMATURE INFANTS.

We know that the act of vomiting in the adult is a complicated one, and is difficult to explain. First there are nausea and salivation followed by

depression of the diaphragm upon the stomach, which increases the negative pressure in the thorax and œsophagus. The fundus ventriculi relaxes, peristaltic movements in the region of the antrum cease ; the pylorus contracts ; the fundus becomes filled with stomach contents, the cardia opens, and under the influence of diaphragmatic pressure reinforced by a convulsive contraction of the abdominal musculature, the stomach muscles contract and the stomach contents are projected into the œsophagus and the mouth, assisted by negative pressure. Whether anti-peristalsis plays an important part in this phenomenon is still a matter of controversy.

How then is this highly complex mechanism set in motion ? If we consult the literature, much of interest both experimental and theoretical may be found. Giannuzzi[5], many years ago, showed that an animal poisoned with curare did not react to an emetic by vomiting, presumably because the abdominal muscles were paralysed. That the diaphragm is also important is shown by the fact that section of the phrenic nerves in animals has an inhibiting action on the occurrence of emesis ; in fact, if the abdominal muscles are at the same time prevented from contracting, the act of vomiting may be entirely suppressed.

Muscular action alone cannot be the sole factor responsible because it has been shown that in spite of intensive muscular pressure, vomiting does not occur when the cardiac sphincter is closed. That an actual sphincter exists at the junction of the œsophagus and stomach is believed by Poulton, Payne, Hurst[6] and others. This sphincter remains closed after a meal and prevents regurgitation of food, gases and gastric juices, which would otherwise occur owing to the gastric pressure associated with the negative thoracic pressure. If this pressure is suddenly raised, the sphincteric resistance is overcome and the cardia opens.

Another important point is the question of nervous control of the stomach. The autonomic intrinsic nerve plexuses of the stomach are under the control of the vagi (chiefly motor in function) and the sympathetics (chiefly inhibitory). Both these nerve trunks seem capable of carrying impulses necessary to start the act of vomiting, and in one and the same animal the same poison may give rise to vomiting by way of different nerve paths. Hatcher and Weiss[4] found that the use of medium doses of digitalis caused vomiting by way of the vagus, whereas strophanthin gave the same result through the splanchnics. The vagus, however, seems to be the chief path by way of which vomiting-promoting impulses are carried. Klee[7] demonstrated that stimulation of the undivided vagus was followed by pyloric closure, opening of the cardia and vomiting. Without going into further detail, it may be stated that more recent experimental evidence points to the fact that the closure of the pyloric valve is chiefly under splanchnic control, whereas the vagi influence the opening of the cardiac sphincter.

In considering the problem of the possible ætiology of true vomiting in the infant, the first point of importance is that the vomiting act differs somewhat from that of the adult. For example, the pressure of the abdominal musculature plays a very small part, and vomiting seems to be a far less unpleasant process, and one more easily initiated than in the adult. There

appears to be little evidence of any accompanying nausea. Atony of the stomach, however, is commonly present and this is perhaps an important predisposing factor to the ease with which vomiting occurs in the infant (Lindberg[11]).

X-ray and clinical investigation show a tendency towards relaxation on the part of the cardiac sphincter in the newborn infant, and this is especially marked in premature and weakly infants. This deficient sphincteric closure is probably associated with atony of the gastric musculature and it is easily demonstrable that after a meal only a slight pressure over the infant's abdomen is necessary in order to cause vomiting. In cases where an infant vomits directly after a meal, the causative agent may be so slight as a contraction of the pyloric antrum unassisted by muscular pressure (Reuss[13]).

Many authors hold that associated with this insufficiency of sphincteric tone there is present a hypersensibility of the gastric mucous membrane. It is worthy of note in this connection that although this is a possible explanation of the vomiting of the neurotic infant, it must not be forgotten that quite a number of normal infants vomit, but rapidly lose this tendency. Another view is that there may be a hypersensitivity towards food to begin with, but as the stomach becomes accustomed to food by repeated fillings, this sensitivity disappears, *i.e.*, a full stomach is therefore a good prophylactic against vomiting (Schick[16]).

The theory that the first fillings of the stomach cause reflex, perhaps anti-peristaltic, contractions of the stomach musculature and thus lead to vomiting, has been advanced, but that anti-peristalsis is a cause of vomiting in the newborn infant is open to doubt. Hess in his experiments was unable to demonstrate it. More recently other observers who were studying vomiting as a result of apomorphine poisoning, noticed that anti-peristaltic waves were visible under X-ray examination. During the process of radiographing an infant with pyloric stenosis, Dr. H. Wimberger, Radiologist to the Pirquet Clinic, and I noted definite anti-peristaltic waves. This was immediately followed by some of the barium feed being shot up into the œsophagus and then slowly sinking back into the stomach : no vomiting occurred.

Unfortunately, the method of investigating vomiting in infants by means of X-rays has its limitations, for it is impossible to subject an infant to the rays for sufficiently long to observe the natural act of vomiting. Especially does this obtain so far as the newborn infant is concerned, because the danger of X-ray injury increases inversely with the age of the child. Again in the case of an infant vomiter, even if one is fortunate enough to witness spontaneous vomiting, the observations are of little value owing to the rapidity with which the act takes place, and the little likelihood of repetition. If we observe, for example, an infant with pyloric stenosis during one of its vomiting bouts, we note that the vomitus is suddenly, rapidly and forcibly ejected. Radiologically we obtain a corresponding picture. The stomach suddenly contracts, too rapidly to allow details to be apparent, and all is over. Such investigatory methods in living infants are, therefore, liable to be difficult and unsatisfactory.

With regard to the nerves influencing the stomach, although the influence of vagi and sympathetics is complicated, we may take it that the vagus is chiefly motor in its action, and the sympathetics inhibitory. H. C. Cameron[1] puts forward the hypothesis that vomiting in the newborn period is facilitated by the absence of a sufficient inhibitory influence. He states that there are several indications pointing to the fact that in earliest infancy the inhibitory activities of the sympathetic are weak and that in the newborn infant, when a large part of the cerebrum is functionless, there may be at times added to lack of inhibition of skeletal musculature a similar weakness of power to inhibit the splanchnic musculature. After all, inhibition, the highest function, is late in development and it seems to be logical to suppose that in the newborn infant such inhibition may be insufficiently developed.

This leads me to the following conclusion as to the possible ætiology of vomiting in the new-born infant :—

The sympathetic system being insufficiently developed, the nervous action in the newborn infant is chiefly vagal with the result that there is a vagotonia. In support of this there is sufficient evidence. This results in a tendency towards increased movements of the gut and, therefore, a tendency towards vomiting. Stimulation of the vagus is followed by relaxation of the cardiac sphincter according to recent investigations, therefore an inhibited vagal action would account for the atony of the sphincter ; and that this atony is important in this connection I am convinced. Compare the ease and comparative, sometimes actual, pleasure with which the infant vomits with the nausea and retching which the adult is compelled to experience in the same act. In the adult a period of nausea is followed by violent contractions of the abdominal musculature with contraction of the diaphragm in order that the act may be completed. To my mind the chief obstacle which the adult stomach has to overcome is the closed cardiac sphincter ; whereas in the infant, owing to insufficiently developed sphincteric control, the cardiac sphincter is readily overcome and vomiting easily occurs.

Carrying this line of explanation further, within the first week of life most normal infants develop sufficient inhibitory (sympathetic) control to stop their tendency to vomit. Premature infants and weaklings require still more time in order to develop this inhibition to a sufficient degree, and the smaller the infant the more time required, and the more difficult the achievement, owing to the facility with which infection takes a grip on an organism weakened congenitally and still further weakened by food loss. Weight is not the only factor concerned, because a premature infant born with comparative constitutional strength which embodies a certain amount of inhibitory control, will more readily tend to survive. Or vice versa, a child of normal birth weight with insufficient or slowly developing inhibitory control will go on vomiting for a longer period than its better equipped brother, and thus lays itself open to the acquisition of habit. Nor is it a long step from such vomiting, if untreated and especially if of a neurotic character, to habitual vomiting.

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